Actual Problems in Chronic Kidney Disease - Mineral and Bone Disorder (CKD – MBD)

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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:

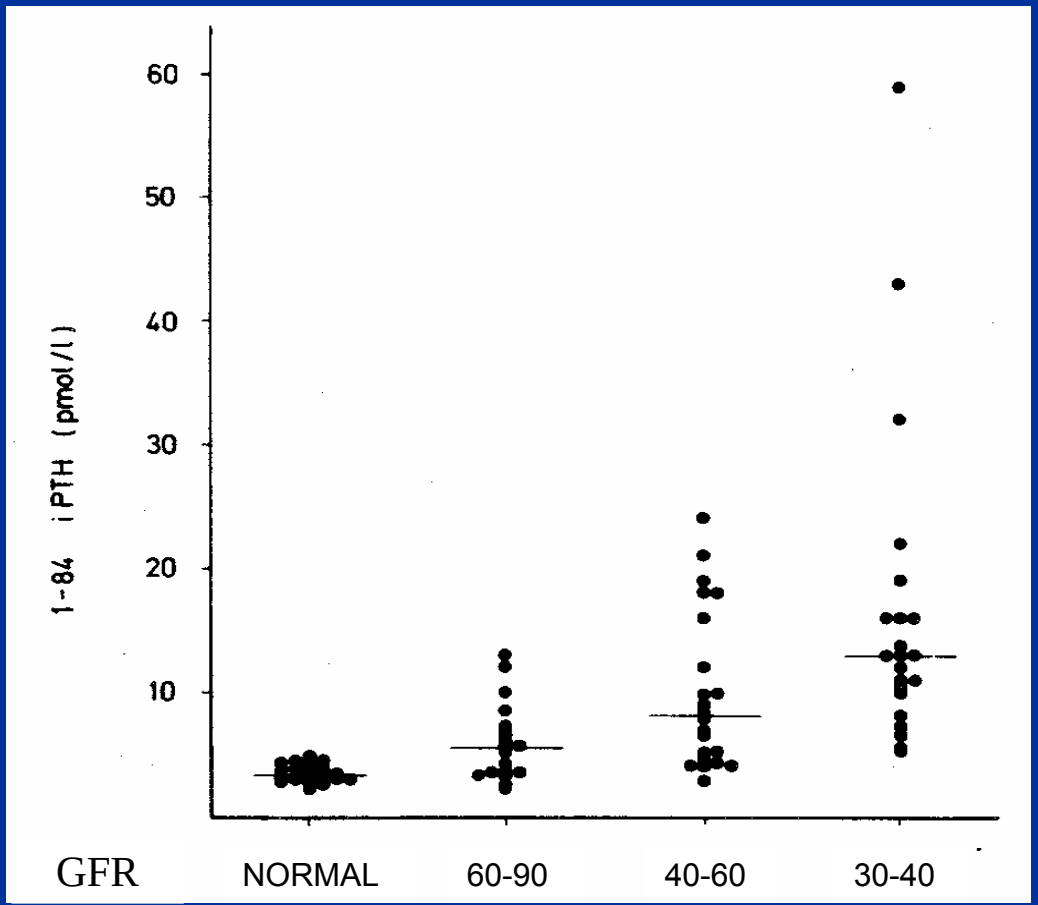
- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or other soft tissue calcification

Moe et al, KI 2006, 69, 1945-53

Outline

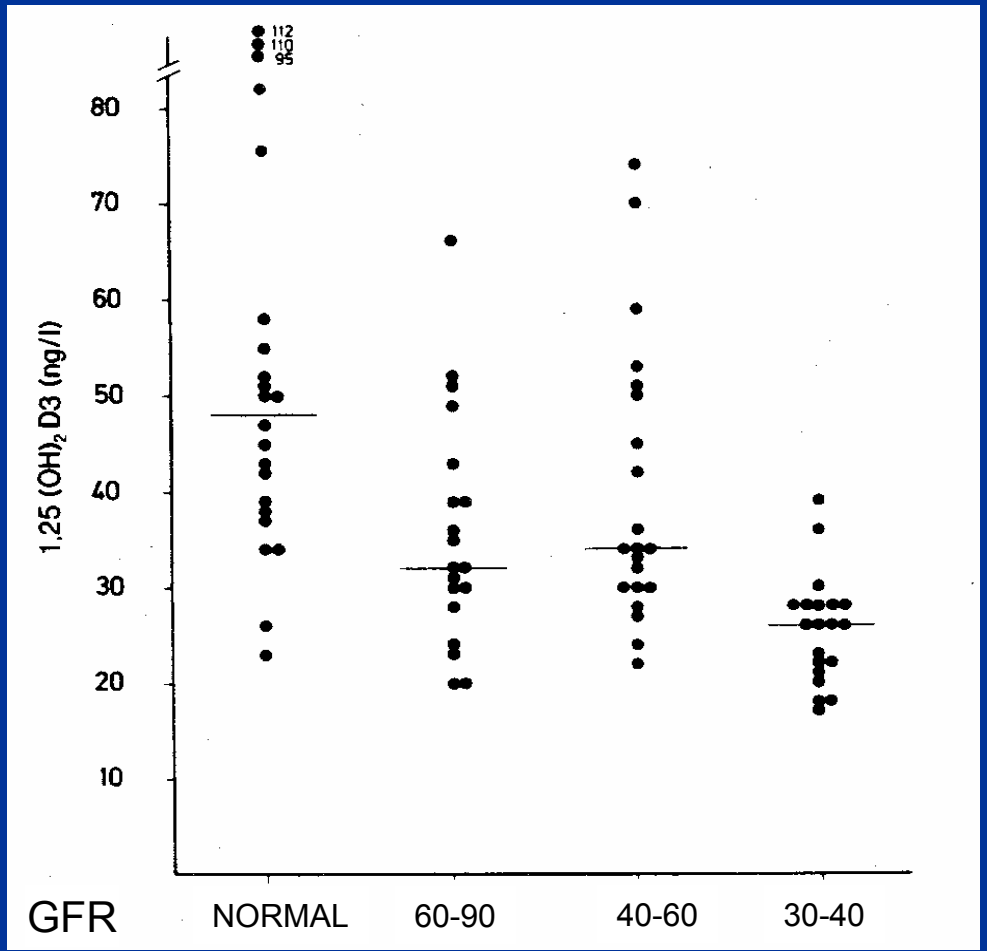
- Regulation of bone modelling
- Vascular calcification and mortality
- Vitamin D deficiency
- Prevention and treatment

GFR and Plasma PTH



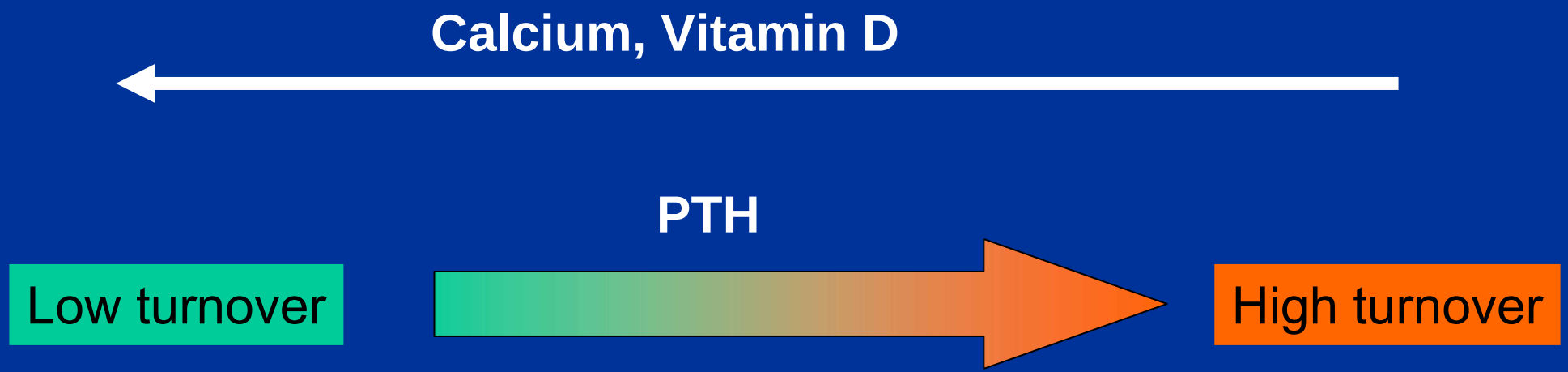
Reichel et al. NDT 1991; 6:162

GFR and Plasma 1,25-Vitamin D3



Reichel et al. NDT 1991; 6:162

Spectrum of Renal Bone Disease

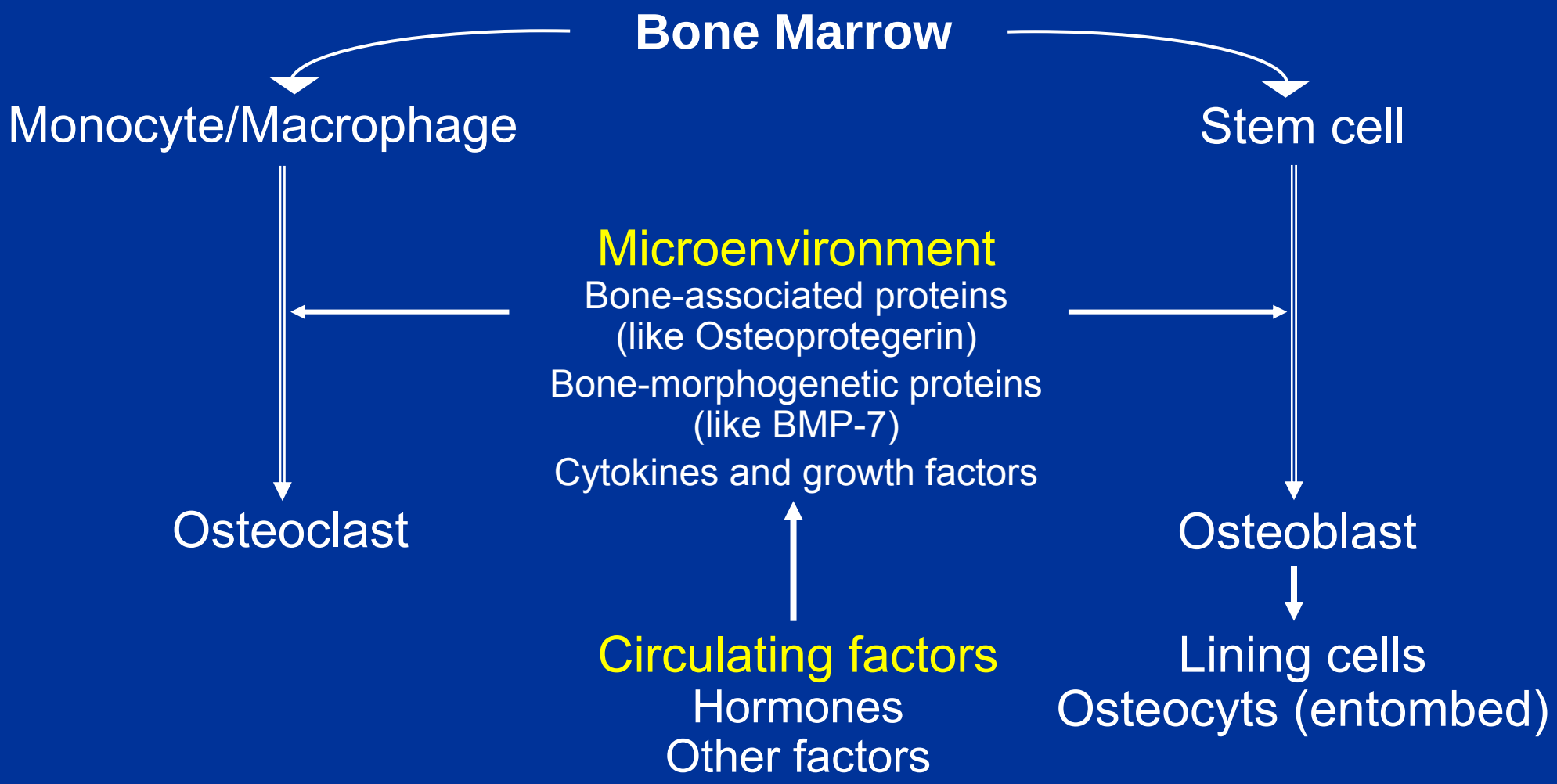


Physiological Doses of PTH and $1.25(OH)_2D$ Do Not Normalize Bone Cells in Uremic Rats

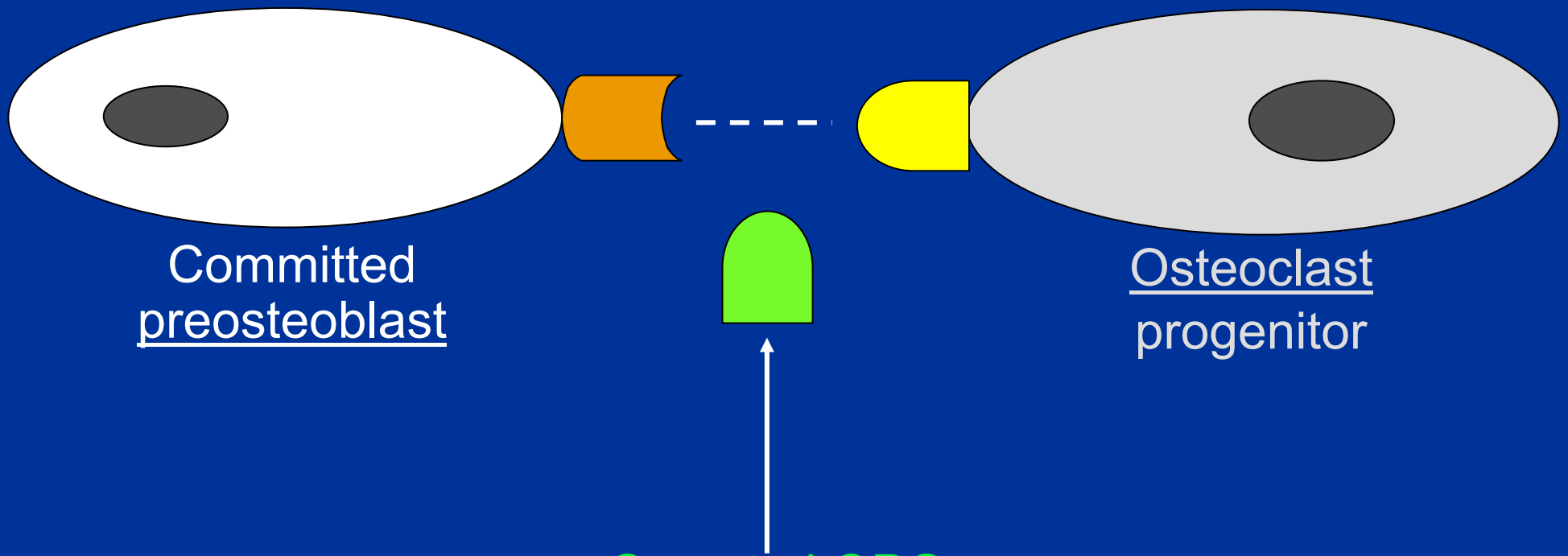
	Sham op *(solvent)*	*NX-PTX* *(solvent)*	*NX-PTX* *(PTH+1.25D)*
S $1.25(OH)_2D$ (pg/ml)	82	56*	77
PTH (pg/ml)	24	5*	23
OcS / BS (%)	6.3	3.7	3.3
ObS / BS (%)	0.8	0.5	1.7

Szabo et al, Eur J Clin Invest 29, 529, 1999

Bone Remodelling
New Concept:Parallel Model



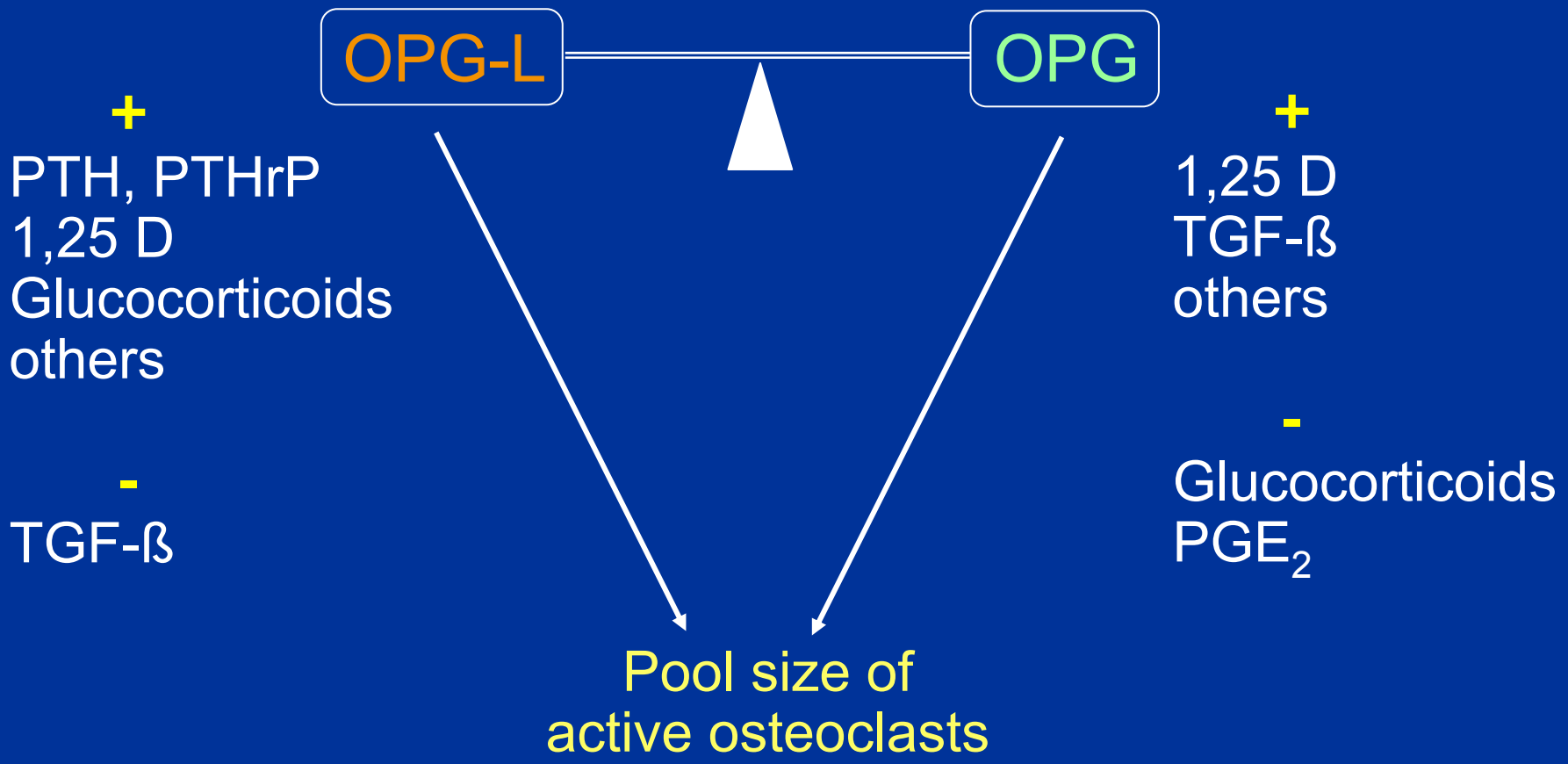
Osteoprotegerin (OPG) Systeme for Osteoclast Differentiation



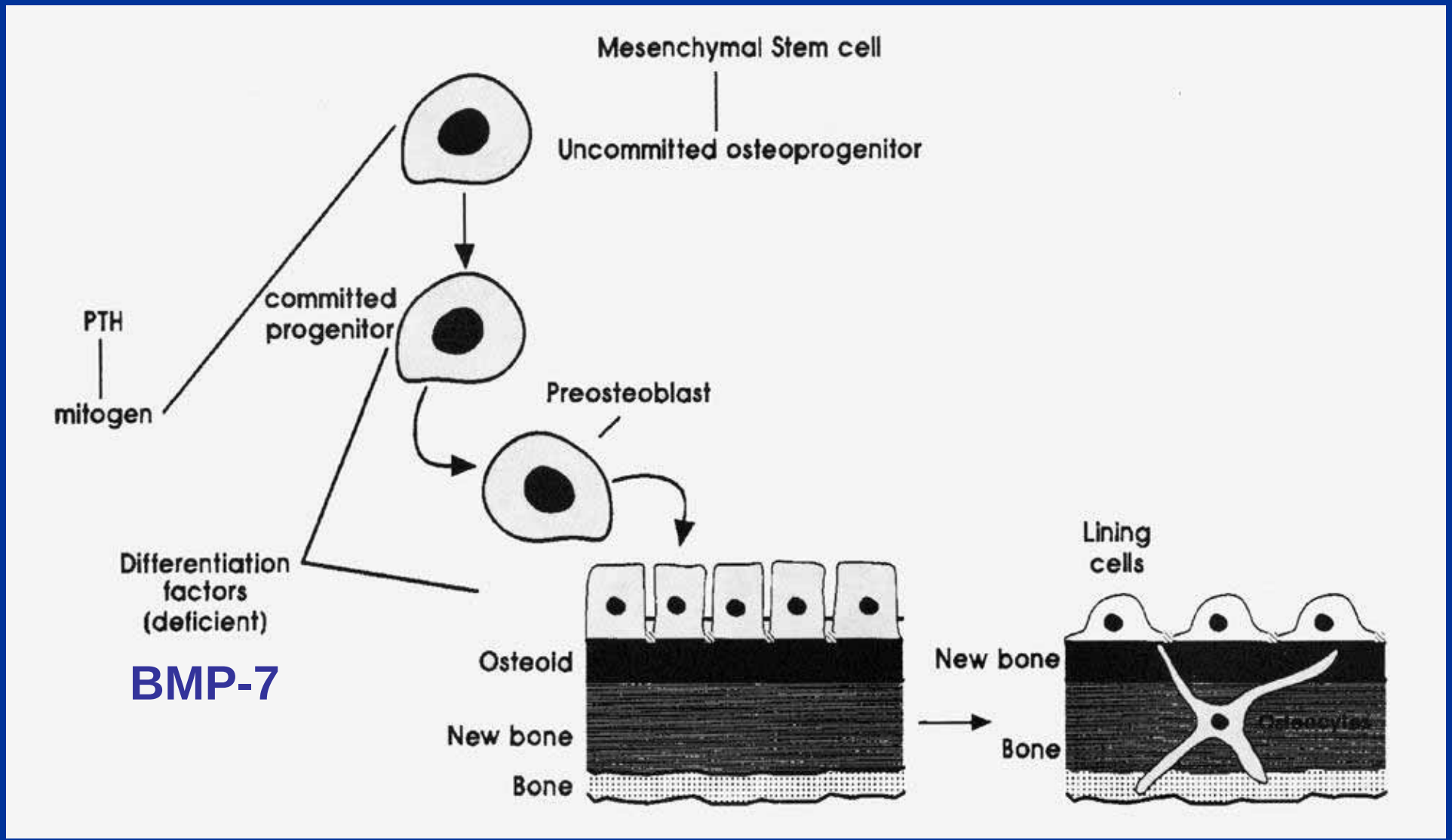
Circulating Osteoprotegerin May Modulate Osteoclastogenesis

1. OPG attenuates the PTH induced rise of serum Ca^{++} *in vivo* (rats)
   OPG decreased serum Ca^{++} rapidly in established hypercalcemia
   Yamamoto et al, Endocrinology 139, 4012, 1998
2. OPG serum levels increased in uremia
   Fukagawa et al, Rinsho Byori 49, 236, 2001
3. OPG serum levels decreased by glucocorticoids
   Sasaki et al, NDT 16, 479, 2001

Regulation of Osteoclastogenesis
Convergence Hypothesis
Hofbauer et al, J Bone Miner Res 15,2,2000



Osteoblast Differentiation Programme



Hruska, Pediatr Nephrol 2000

BMP-7 (Differentiation Factor)
Rh BMP -7 is available

Decreases glomerular area, glomerulosclerosis and interstitial nephritis

Hruska et al, J Am Soc Nephrol 13, 45A, 2002

Inhibits monocyte chemoattractant protein-1 (mesangial cells) and renal injury

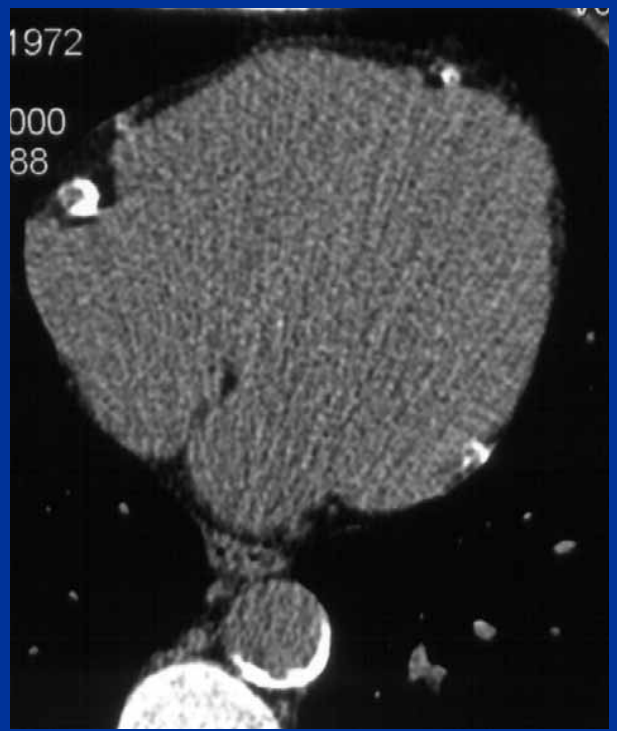
Yong-Soo Kim, J Am Soc Nephrol 13, 353A, 2002

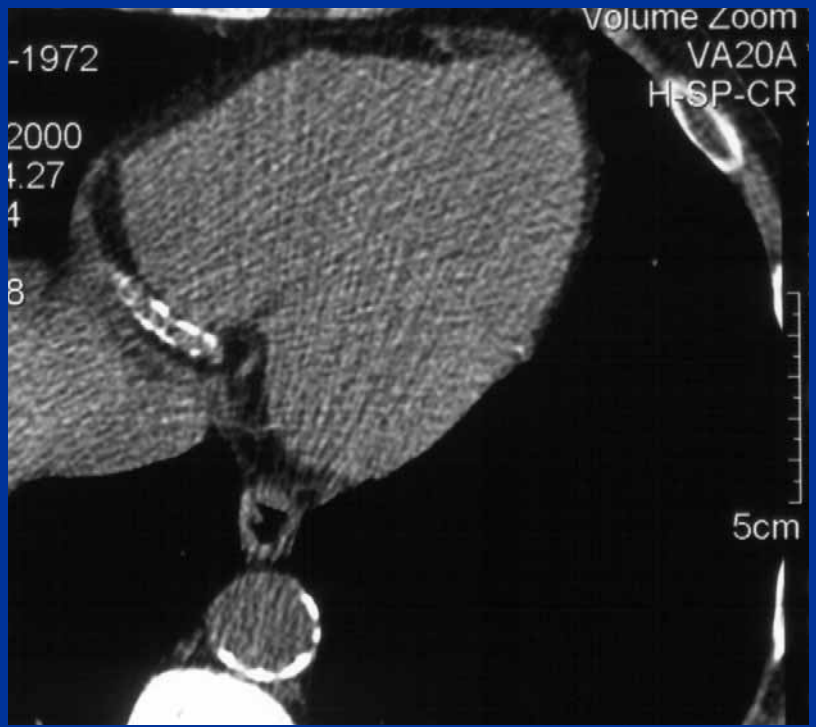
Reverses adynamic bone disease and lowers serum PO_4

Hruska et al, J Am Soc Nephrol 13, 578A, 2002

Vascular Calcification

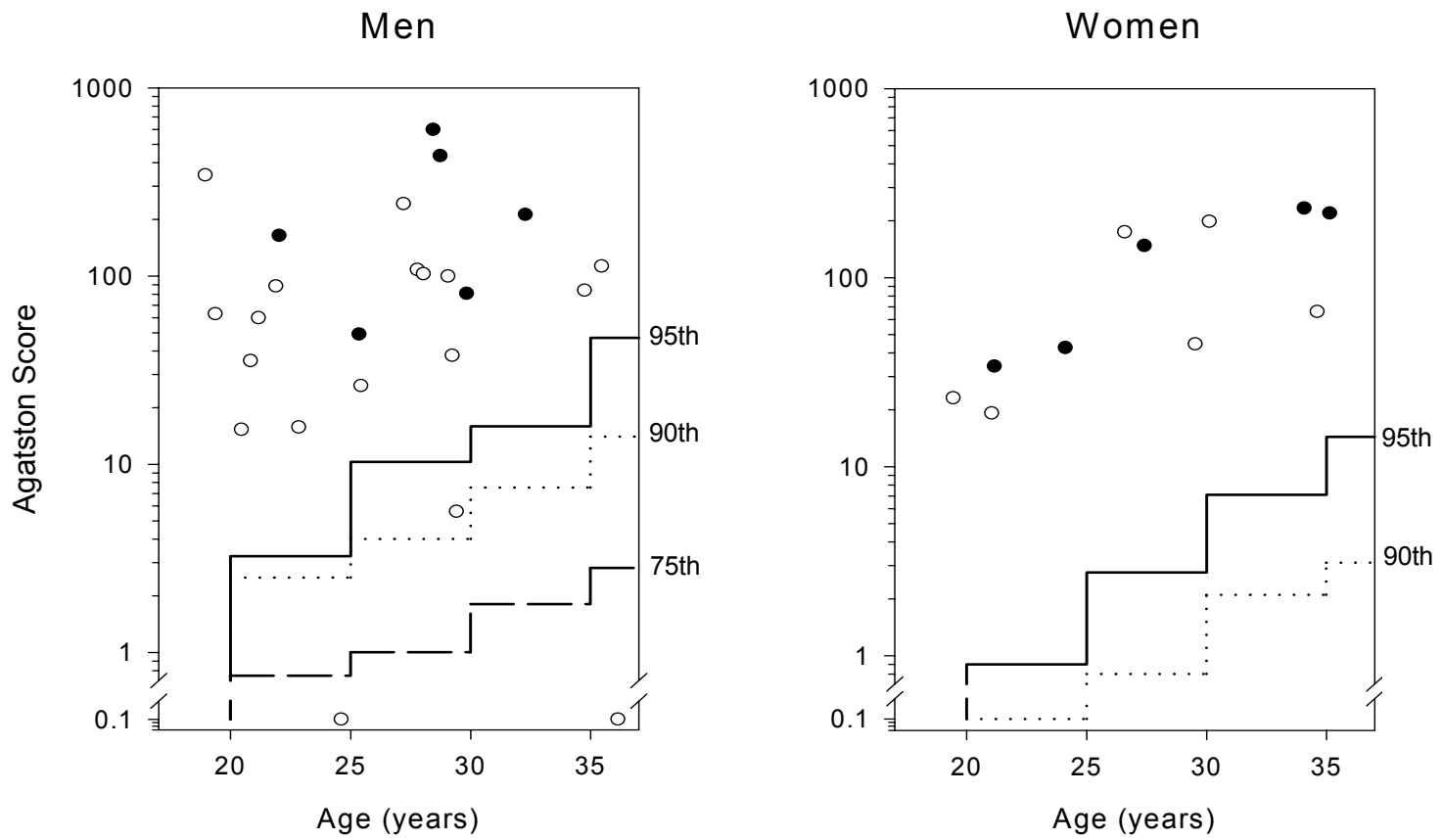
Three-Vessel Coronary Artery Disease and Aorta Calcification in a 28-year-old Hemodialysis Patient with Childhood-Onset CRF





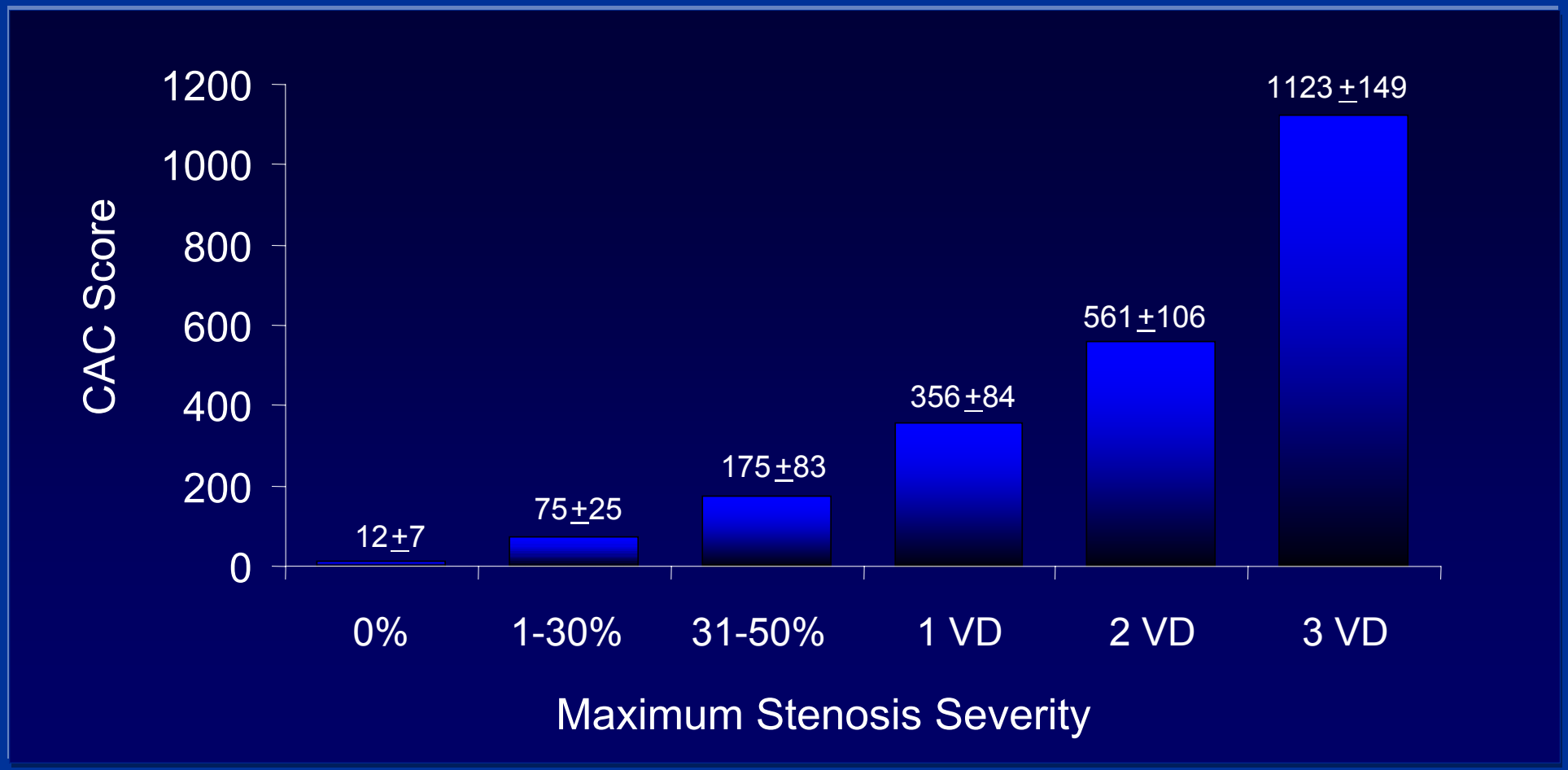
Oh et al. Circulation 2002;106:100-5

Coronary Artery Calcifications in Young Adults with Childhood-Onset ESRD



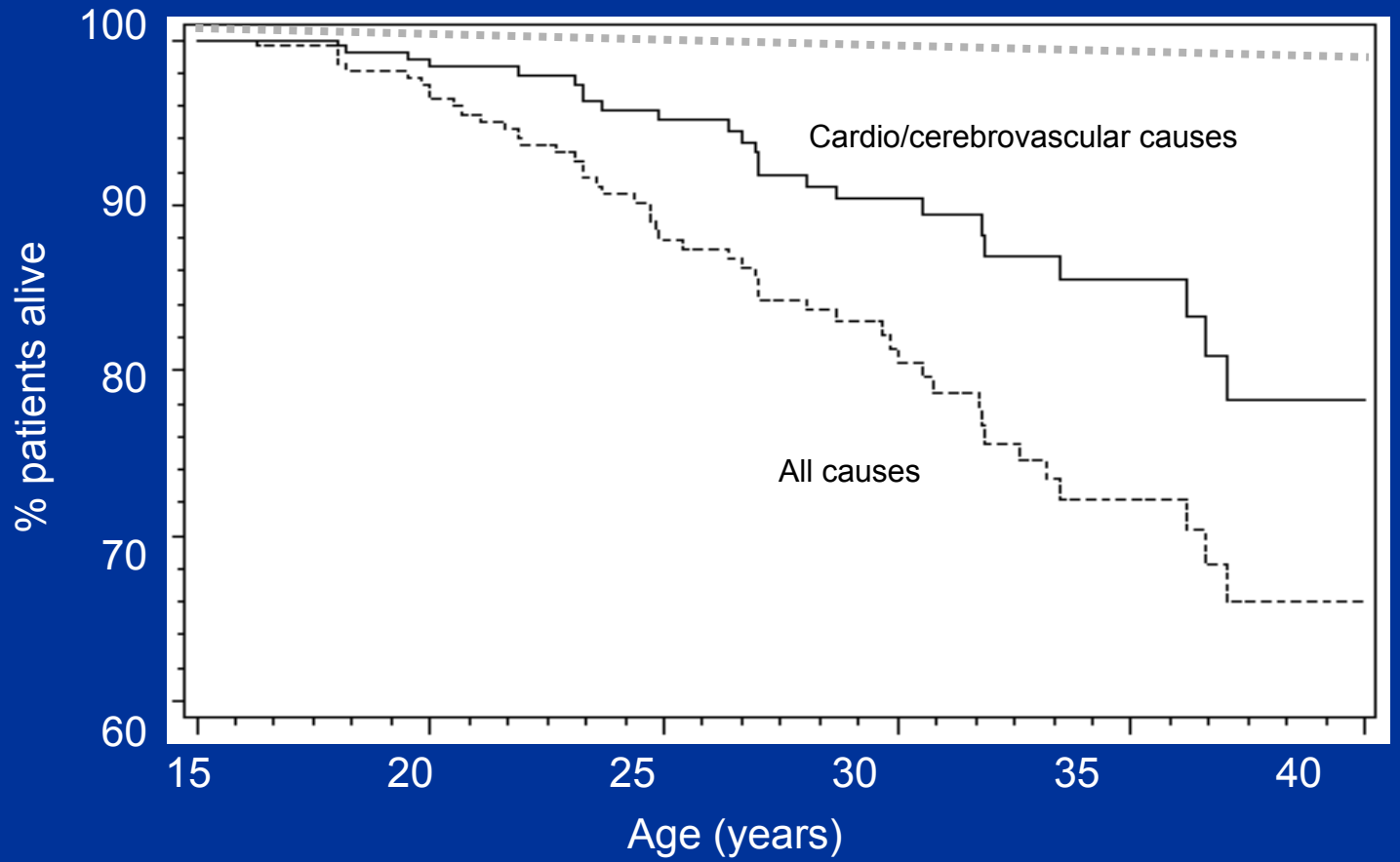
Oh et al. Circulation 2002;106:100-5

EBCT Calcium Score and Angiographic CAD Severity



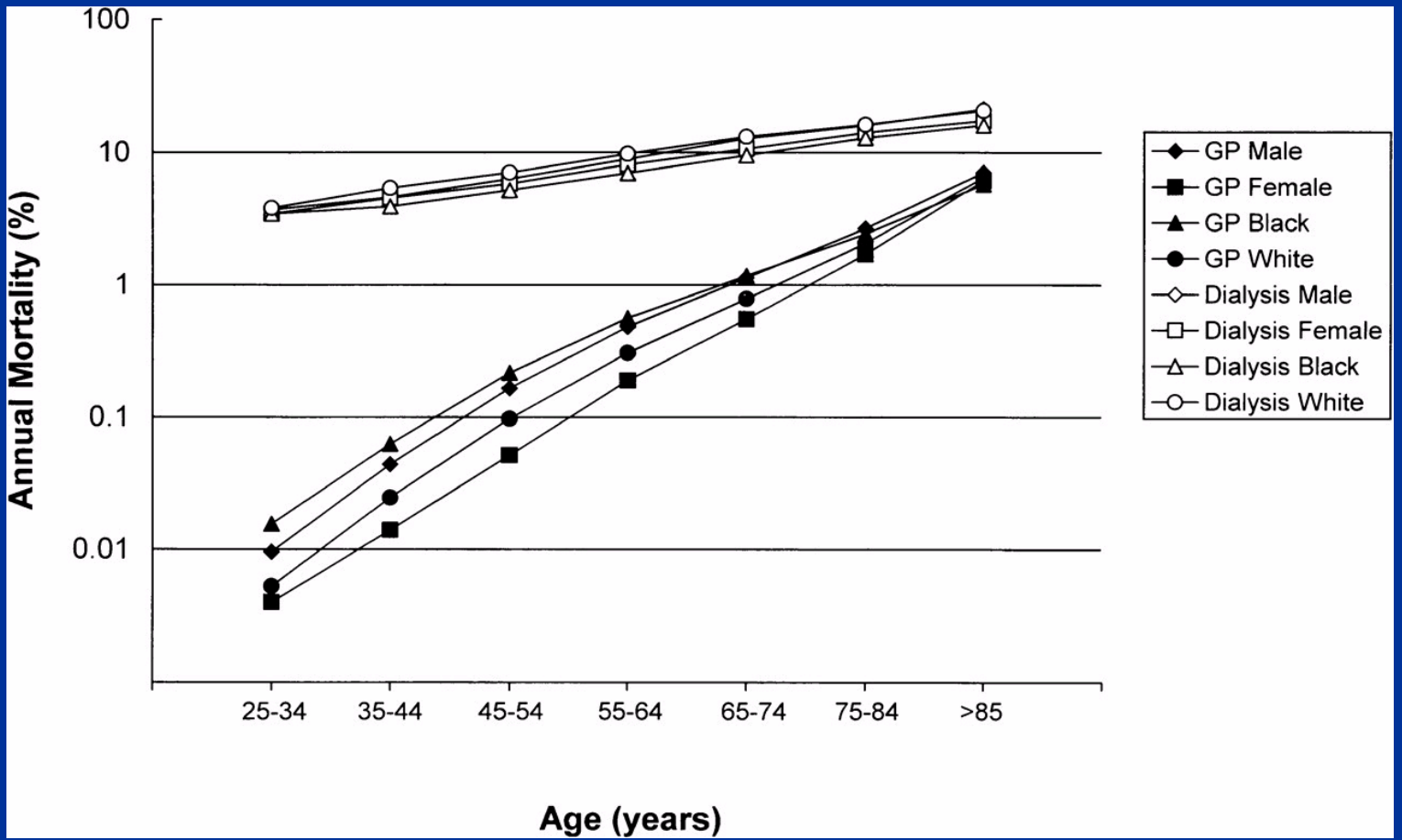
Courtesy of John Rumberger, MD, Mayo Clinic

Long-Term Survival of Childhood-Onset ESRD Patients



Oh et al. Circulation 2002;106:100-5

Excessive Mortality in Young Adults with ESRD



Block et al. AJKD 2000

ESRD-Associated Arteriopathy:

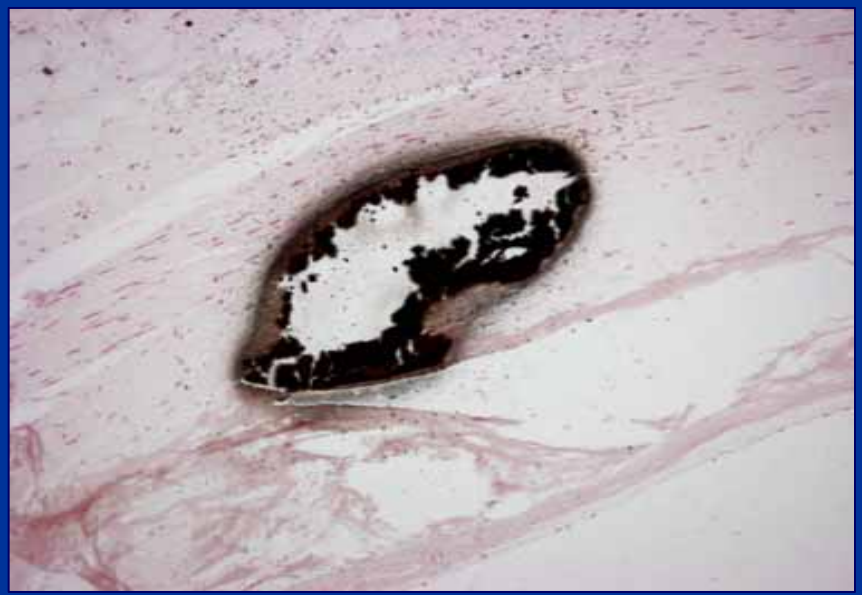
Accelerated Atherosclerosis or

Disease-Specific Pathology?

Arteriopathy in Adults with ESRD

Schwarz et al. NDT 2001

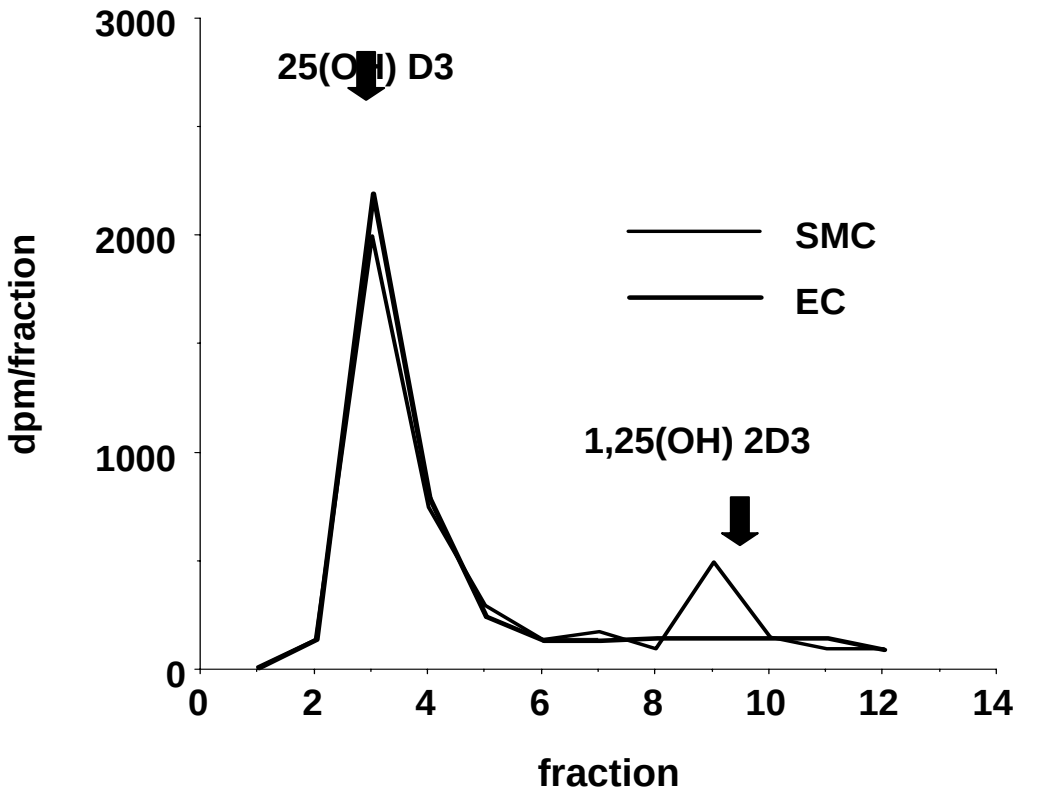
- Mönckeberg-Type Media Degeneration
- Minor Intimal Hyperplasia
- Increased Calcification of Atherosclerotic Plaques
- Diffuse Calcinosis of Tunica Media



Vitamin D

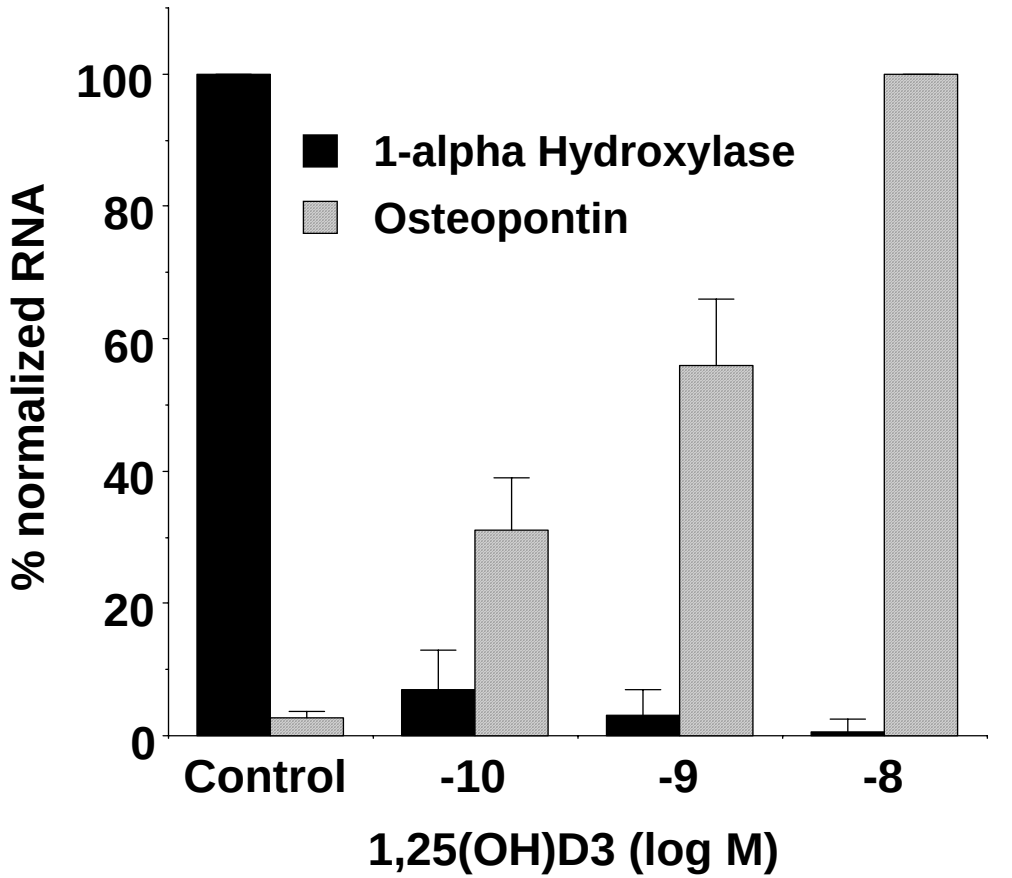
Does it contribute to vascular calcification?

Smooth Muscle Cells Produce Calcitriol



Dengler et al (unpublished)
Somjen et al.Circulation 2005

Expression of 1α-Hydroxylase and Osteopontin in Smooth Muscle Cells



Effect of Calcitriol on Vascular Calcification

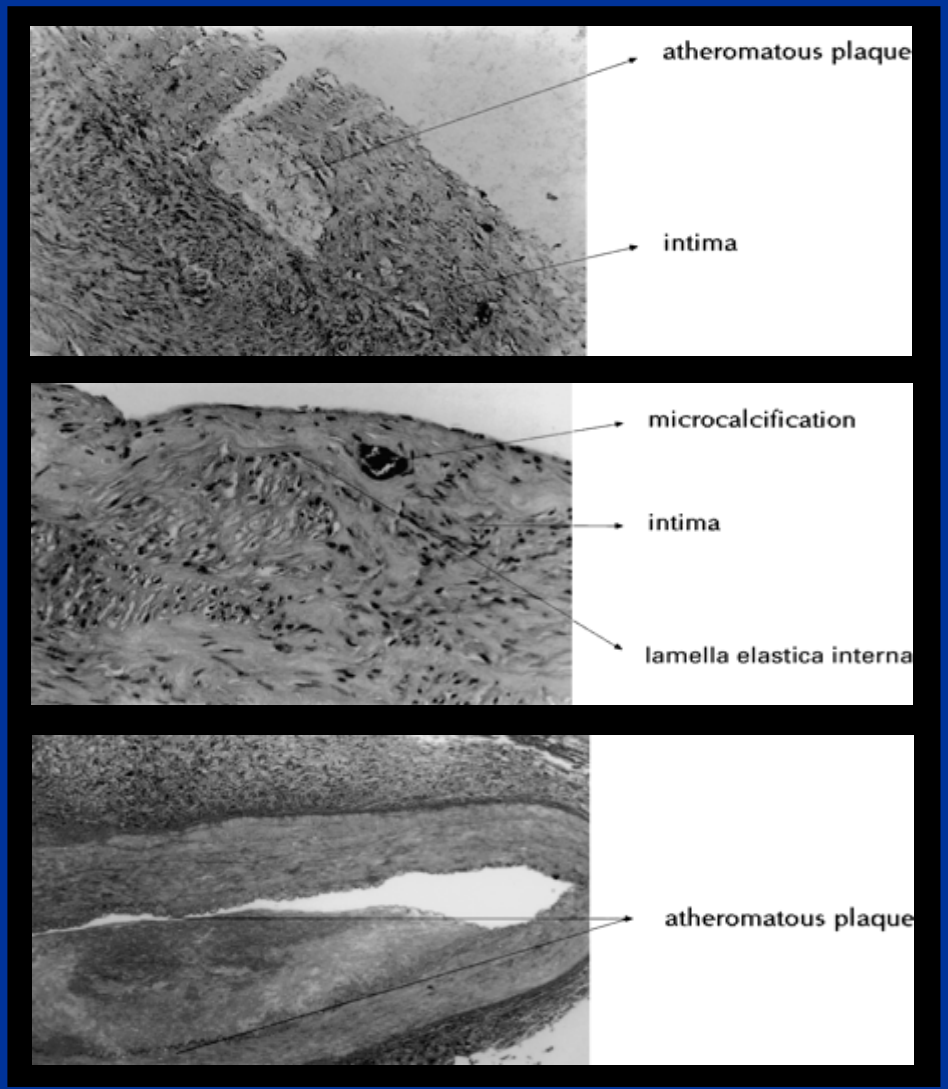
- Vit.D intoxication leads to media calcification
- Vascular smooth muscle cells express Vit.D-R
- Vit.D may initiate mineralization in an osteoblast-like phenotype cell
- But , ……

Effect of Calcitriol against Vascular Calcification

- Calcitriol levels are inversely correlated with coronary calcification
  Watson et al, Circulation 96, 1755, 1997

- Vit.D upregulates matrix GLA protein in osteoblasts and smooth muscle cells
  Frazer & Price, Calcif Tissue 46, 270, 1990
  Shannan et al, Crit Rev Eukaryot Gene Expr 8, 357, 1998

Atherosclerosis in Adolescents with ESRD



Nayir et al. NDT 2001; 16: 2041

Iliac artery specimens obtained at TX
Age: 12-17 yrs
Mean duration of hemodialysis: 2.3 yrs

Atherosclerotic lesions in 7/12 pts
Hypoplastic/reflux nephropathy in 6/7

Predictors of arterial lesions:
Disease Duration
Serum phosphorus
Ca x P product

Not predictive:
Blood pressure
Fasting glucose
Triglycerides, cholesterol

Predictors of Coronary Artery Calcification

Stepwise Linear Regression Analysis

Variables offered to model:

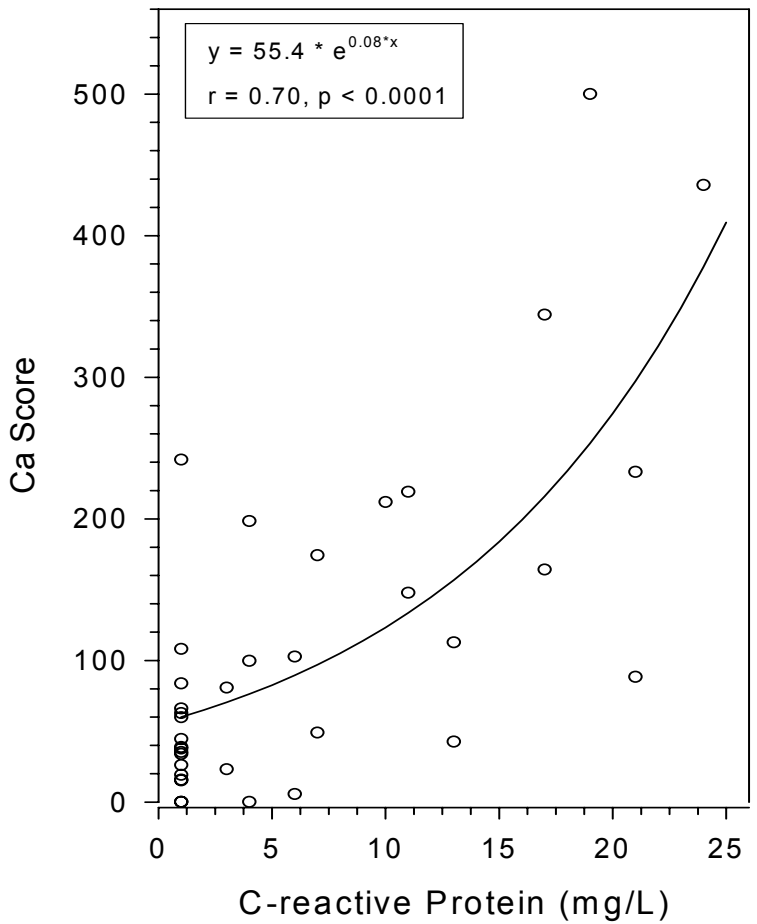
Current age, sex, BMI, current treatment modality, CRP, Hba1c, C peptide, homocysteine, CRP, C. pneumoniae IgG; total, LDL-, HDL-cholesterol

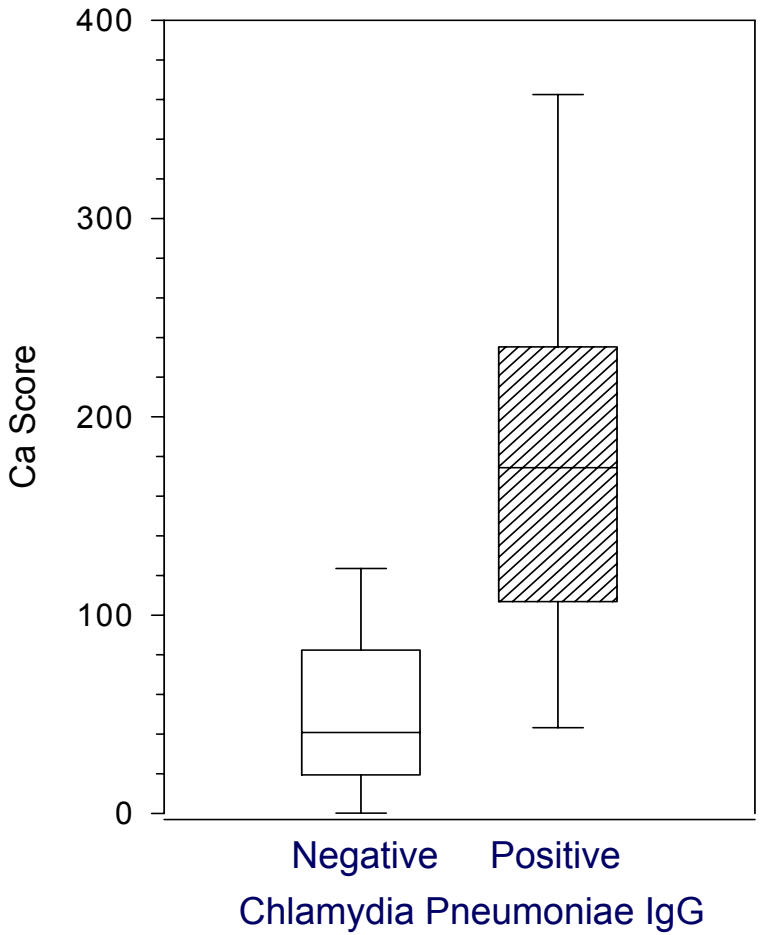
Cumulative duration of CRI, dialyis, transplant; Ca*Ph, PTH, blood pressure

Variables selected:

	Effect	Partial R^2	Total R^2	P
CRP	Positive	0.5	0.50	<0.0001
Mean PTH	Positive	0.15	0.65	0.0006
Mean (Ca*P)*ESRD	Positive	0.07	0.72	0.01
Homocysteine	Positive	0.03	0.75	0.05

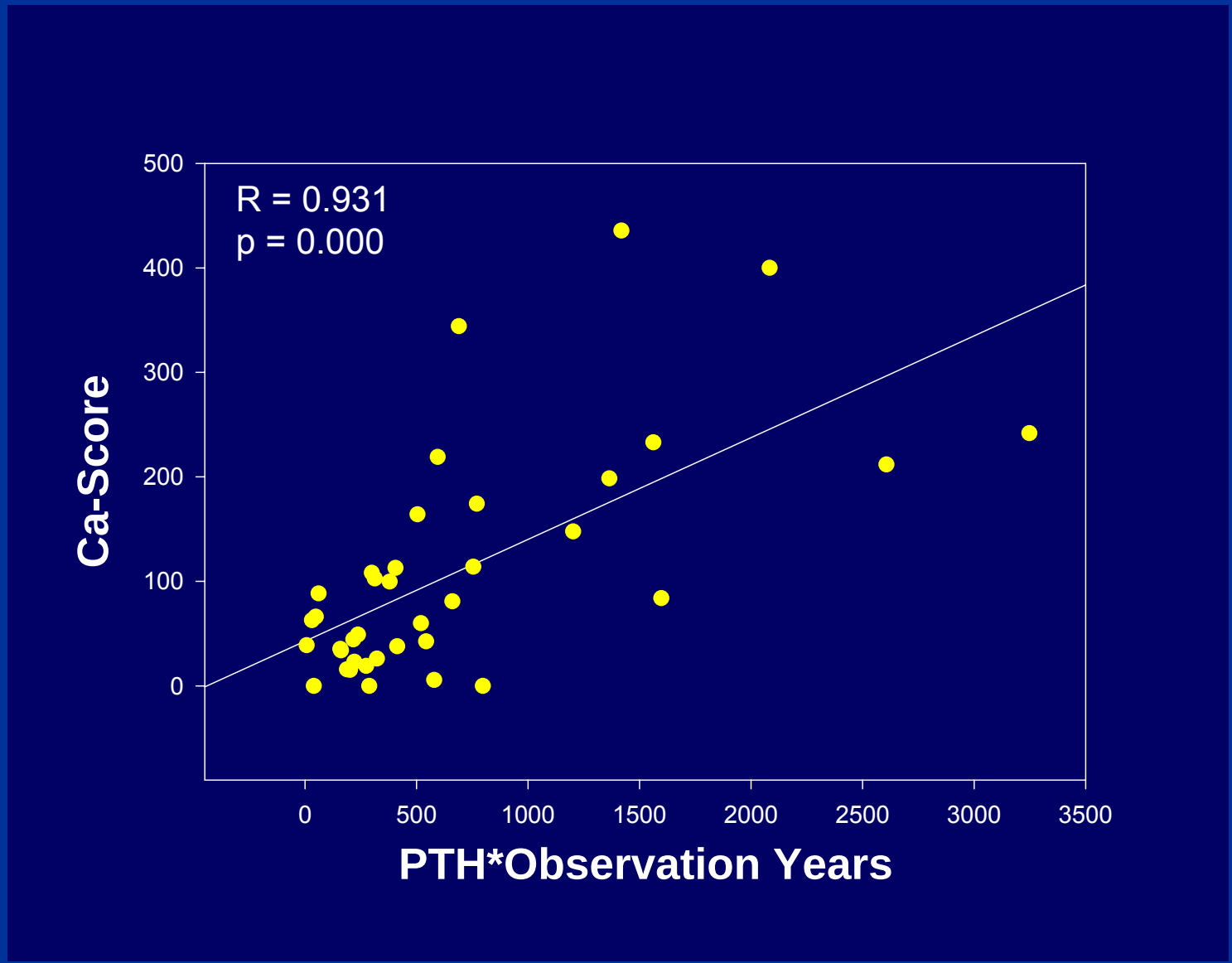
Inflammation and Coronary Calcification in Childhood-Onset ESRD



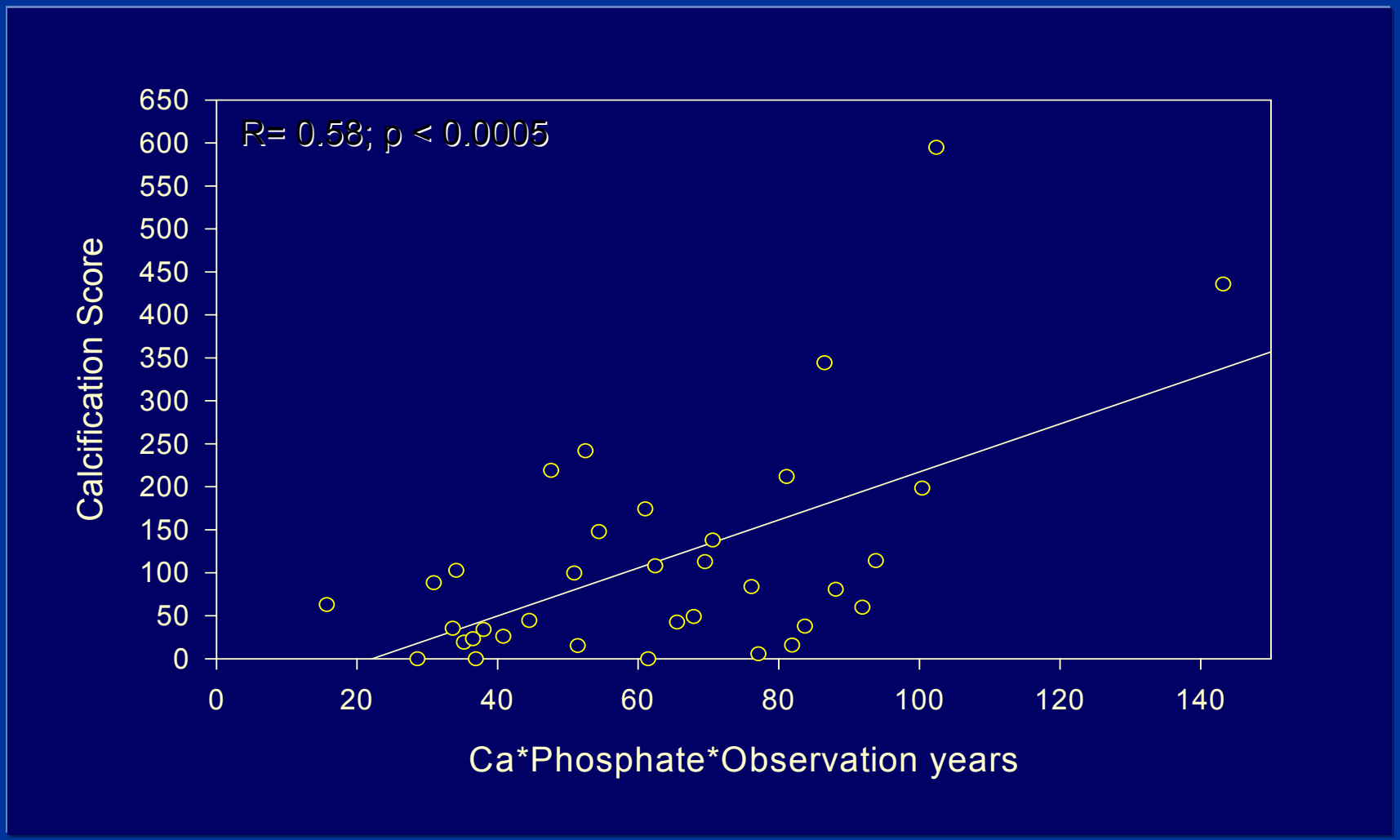


Oh et al. Circulation 2002;106:100-5

Coronary Calcifications and Cumulative PTH



Coronary Artery Calcifications and Cumulative Ca*P Load



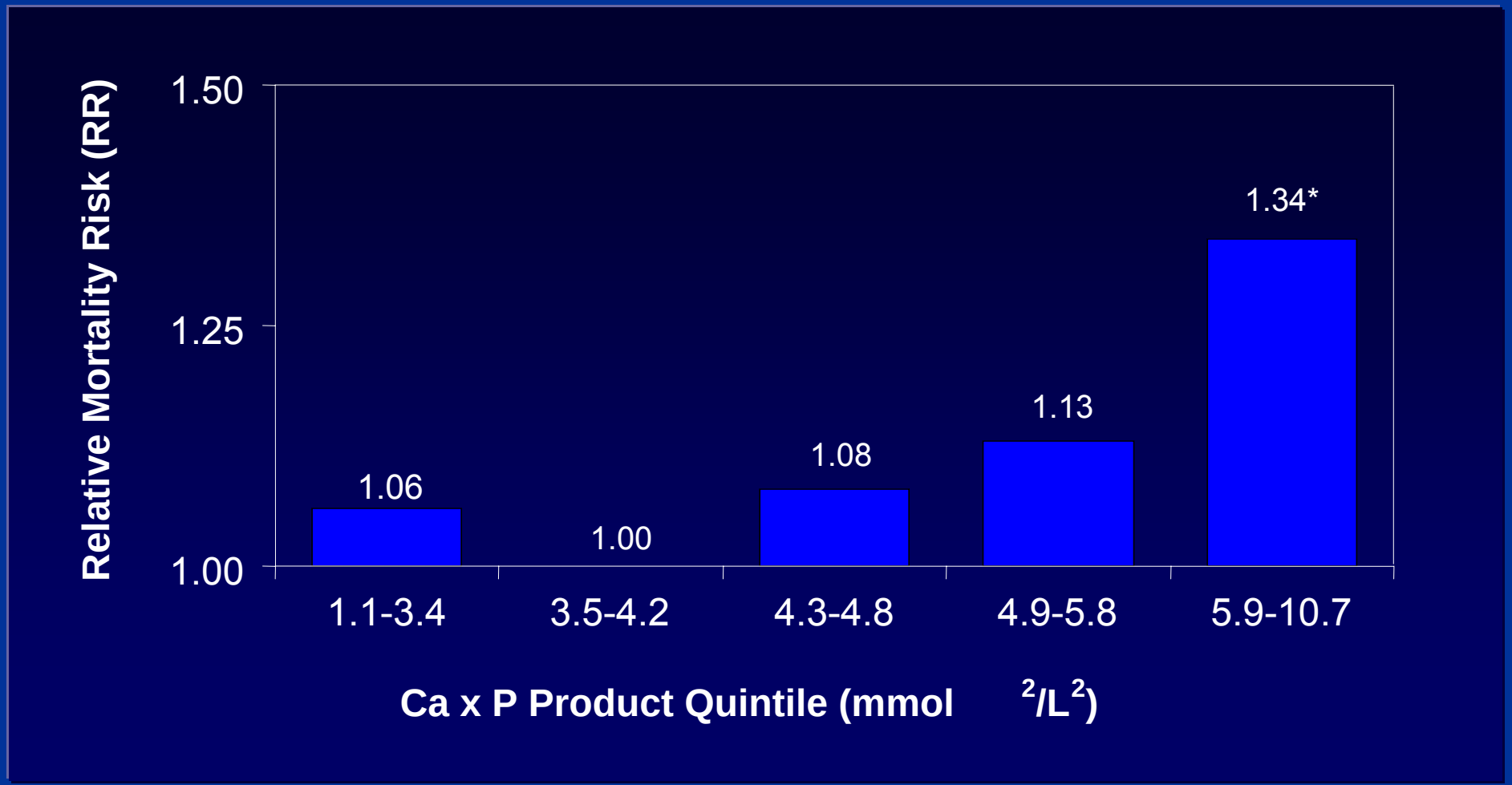
Potential Risk Factors for Coronary Calcifications

Univariate Regression Analysis

Heidelberg study

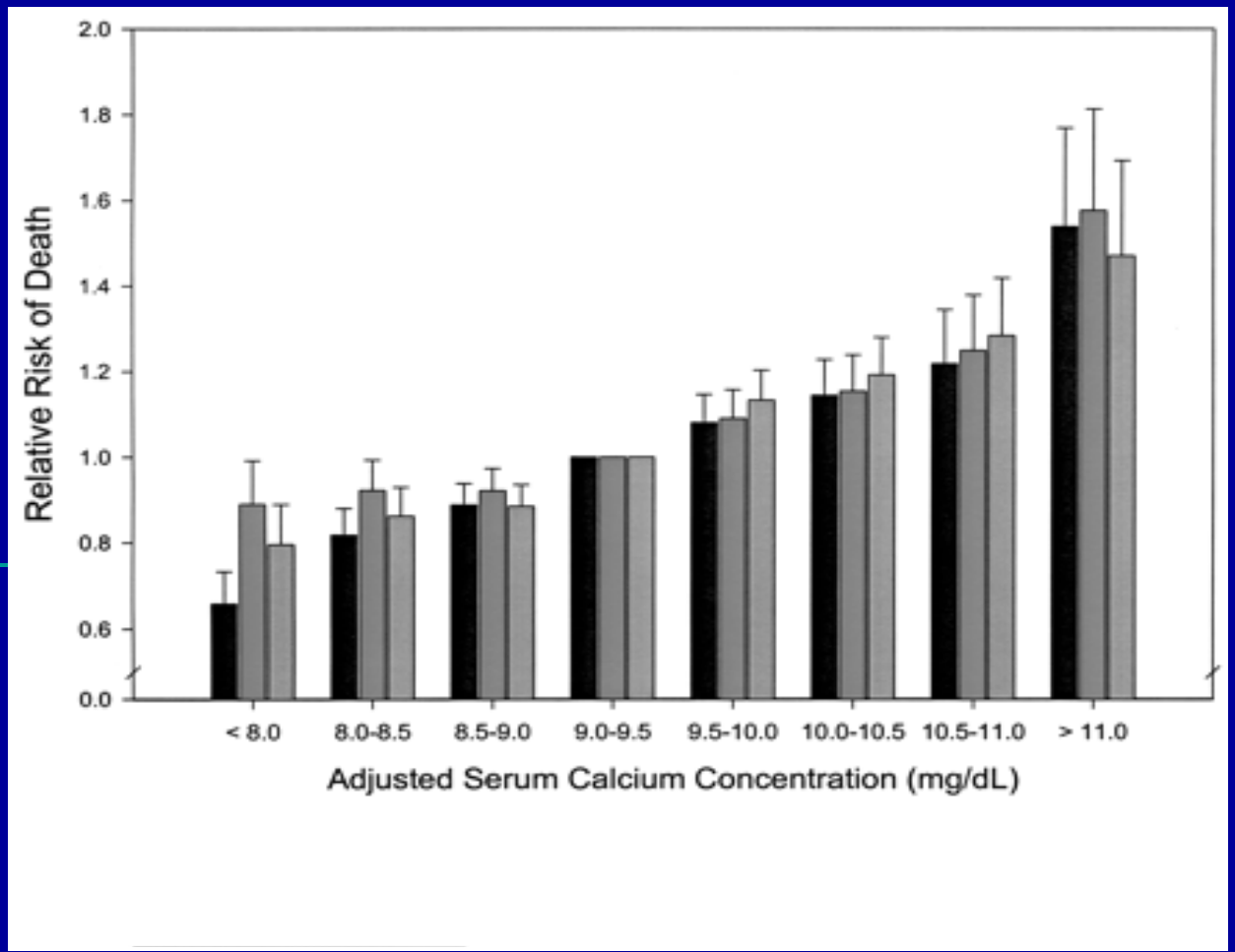
	R	p
CRP (mg/L)	0.62	< 0.0001
Mean PTH (µmol/L)	0.62	< 0.0001
ESRD (years)	0.59	0.0007
Cumulative time on dialysis	0.33	0.04
Cumulative Ca*P (mg/dl)	0.58	0.0005
Cumulative P (mg/dl)	0.30	0.06
Serum homocysteine (µmol/L)	0.35	0.03
Cumulative Ca (mg/dl)	0.38	0.02

Elevated Ca*P Product Increases Mortality Risk



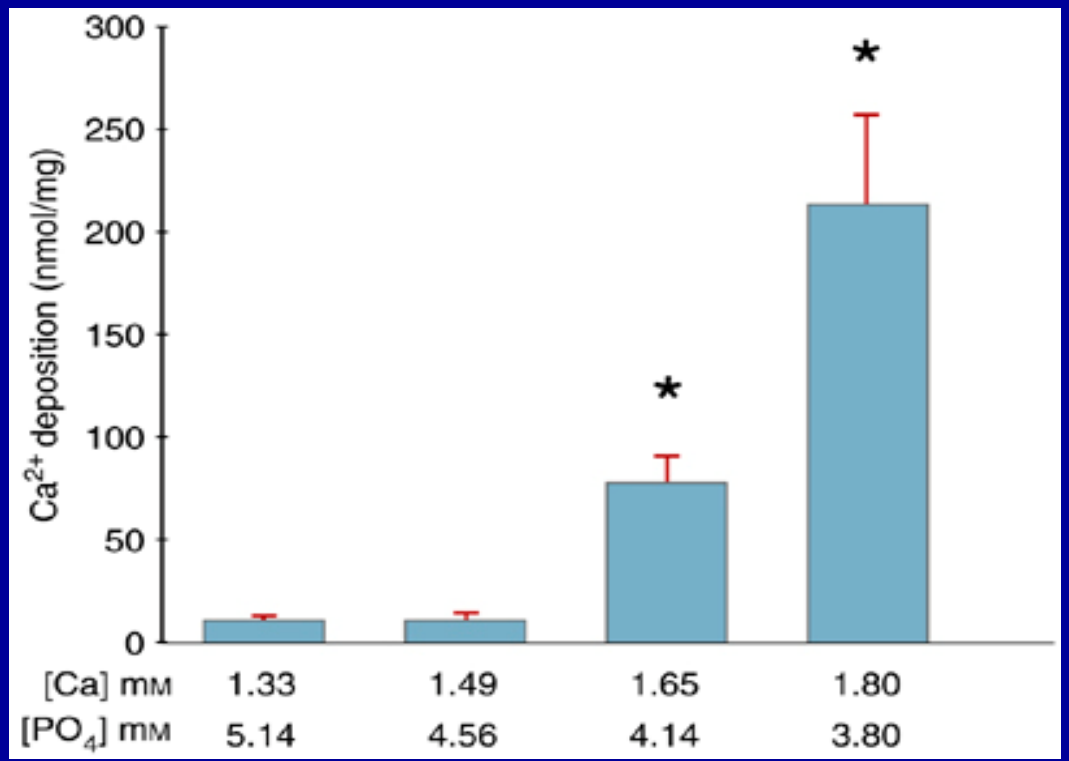
Block et al. AJKD 1998; 31:607-17

Relative Risk of Mortality by Serum Calcium



Block et al, J Am Soc Nephrol 2004, 15, 2208-2218

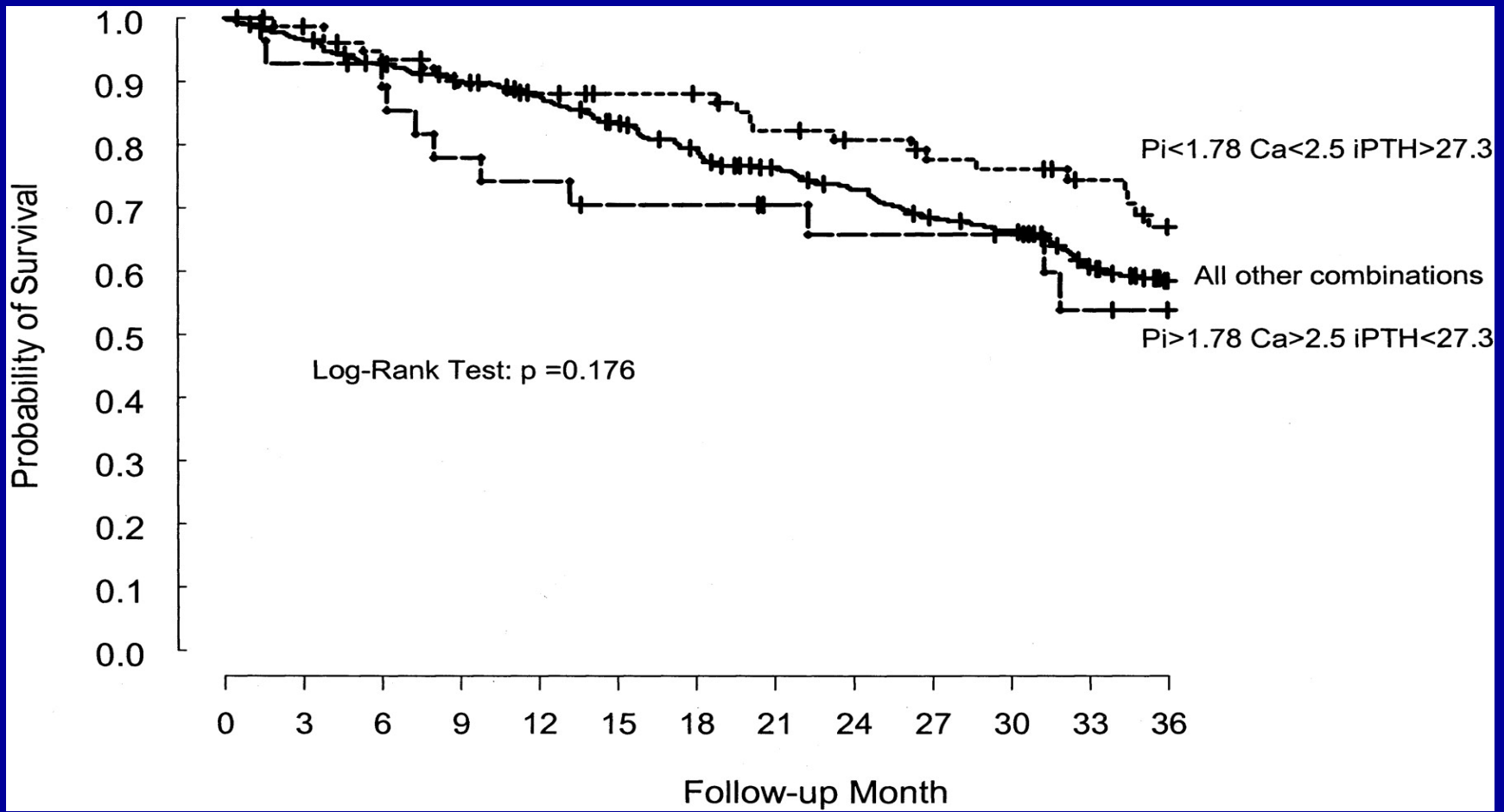
Calcification of Rat Aorta at a Constant Ca x P Product



Lomashvili et al, Kidney Int 2006, 69, 1464-70

O'Neill Kidney Intern ,2007 ,in press

Survival as a Function of Ca, P, PTH



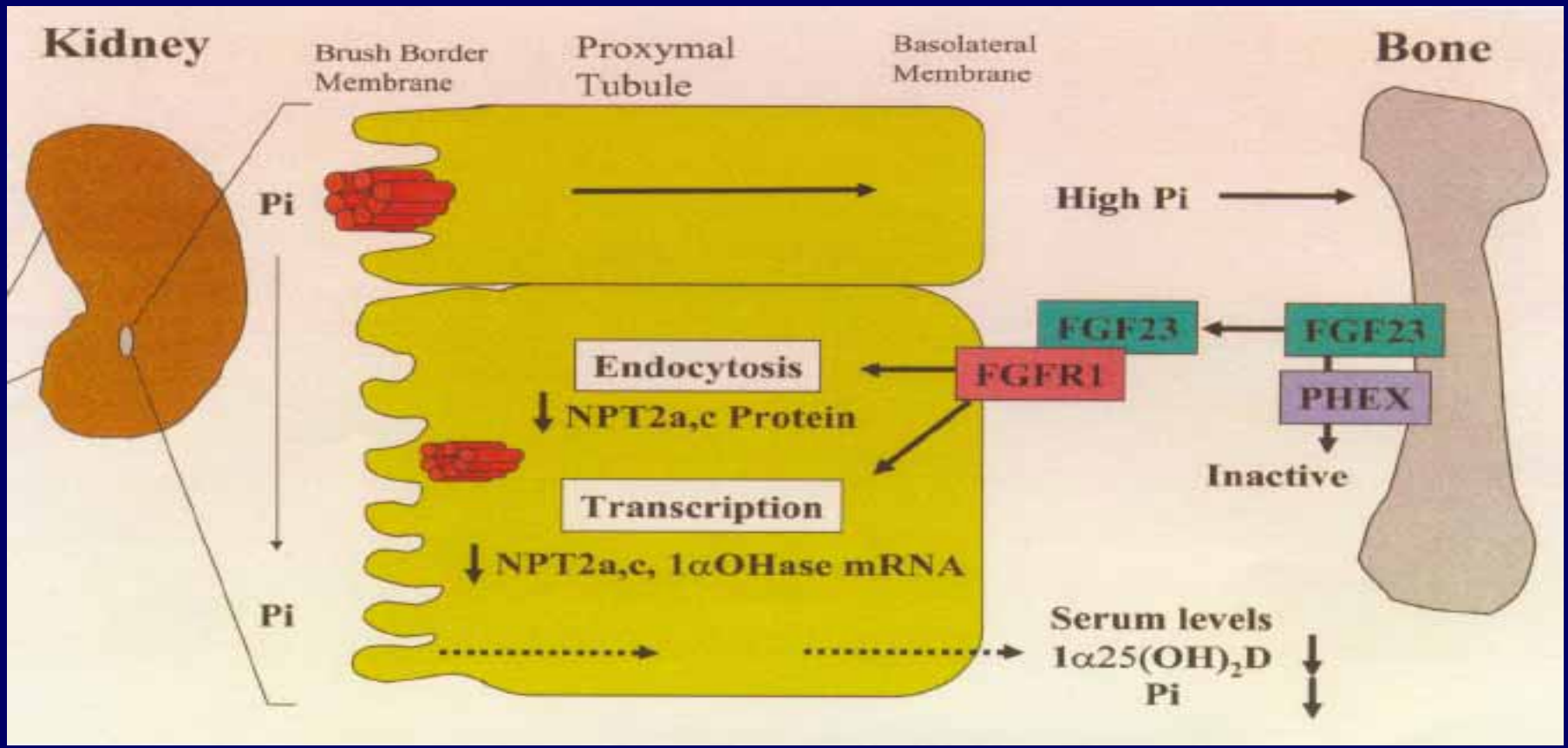
Stevens et al, J Am Soc Nephrol 2004, 15, 770-9

Effects of Hyperphosphatemia

- Induction of hyperparathyroidism
  - directly (parathyroid gland)
  - indirectly
- Reduces circulating 1,25(OH)D
  - directly (renal 1α-hydroxylase)
  - indirectly (stimulates FGF-23 which down-regulates 1α-hydroxylase)
- Contributes to vascular calcification

  Mechanism?
- Non liner correlation with morbidity

Phosphate Homeostasis Regulated by FGF23



Takeda et al, J Cell Mol Med 8, 191-200, 2004

Effects of Hypercalcemia

- Decreases PTH secretion
- Decreases 1α-hydroxylase
- Contributes to vascular calcification mechanism?
- Induces low bone turnover
- Linear correlation with morbidity

Mechanisms for Vascular and Cardiac Calcification

- Adynamic bone $\rightarrow$ decreased bone buffer for Ca and P $\rightarrow$ precipitation ?
  Kurz et al, Kidney Int 46, 855, 1994
- Passive process in need of inhibitors
  Schinke & Karsenty, NDT 15, 1272, 2000
- Active processes rather than precipitation
  David & Hruska, Kidney Int 60, 472, 2001

Promoters and Inhibitors of Vascular Calcification in the Microenvirement of vessel wall

Promoters: BMP-2
Cbfa-1 (acting on osteocalcin)

Inhibitors:

- circulating: BMP-7
Fetuin-A
Pyrophosphate

- locally acting: Matrix Gla protein
Osteocalcin
Osteopontin
Osteoprotegerin
PTHrP
Pyrophosphate

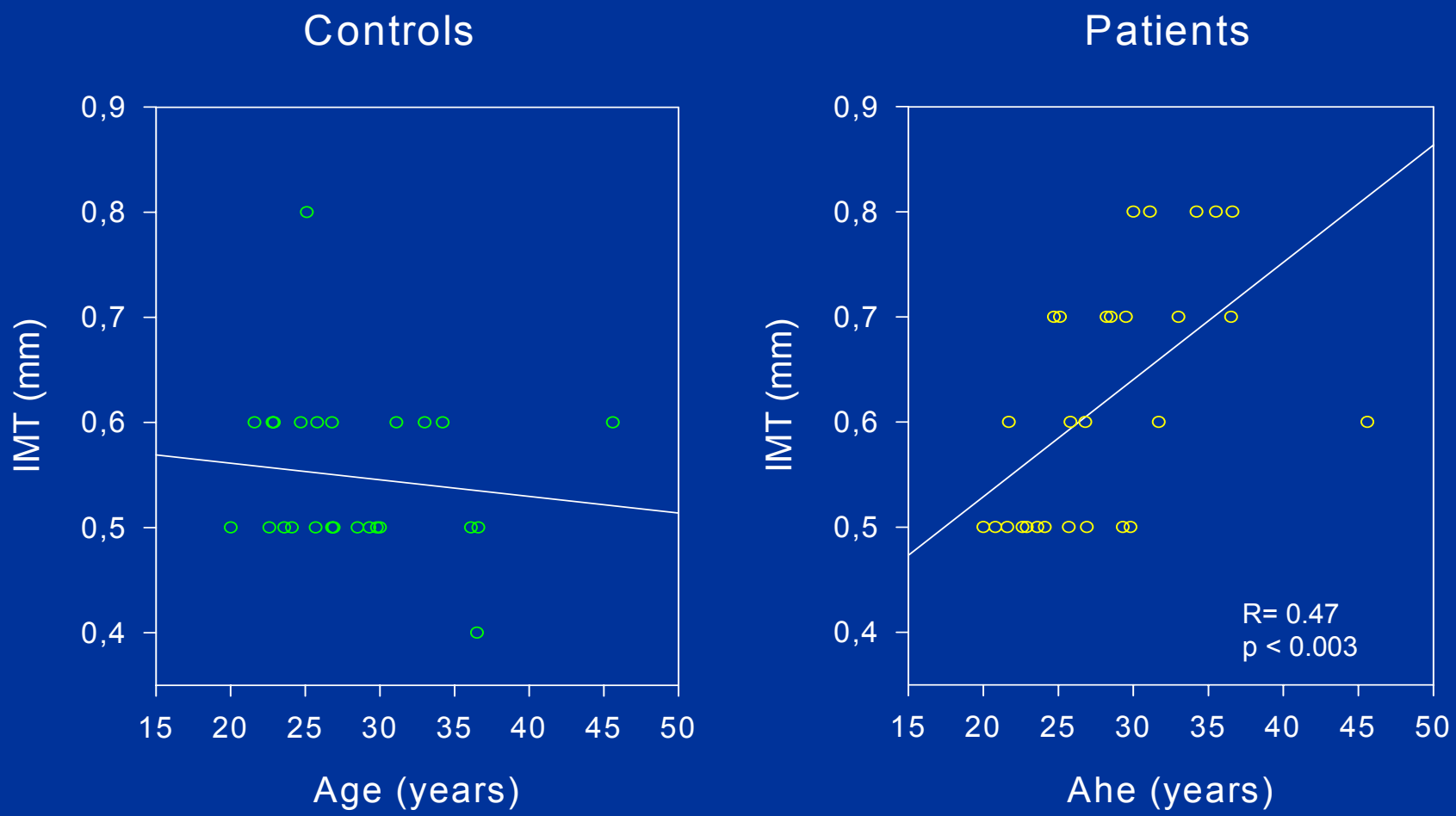
Pathogenesis of Vascular Calcification
A Central Role for an Osteoblast-Like Cell

Pericytes and smooth muscle cells

- are derived from common marrow mesenchymal stem cells like osteoblasts
- retain their pluripotentiality and have the capability to become osteoblasts

Campbell & Campbell, Z Cardiol 89 (SII), 54, 2000

Age-Dependent Carotid Intima Media Thickness in Young Adults with Childhood-Onset ESRD



Oh et al. Circulation 2002;106:100-5

Predictors of Carotid Intima Media Thickness

Stepwise Linear Regression Analysis

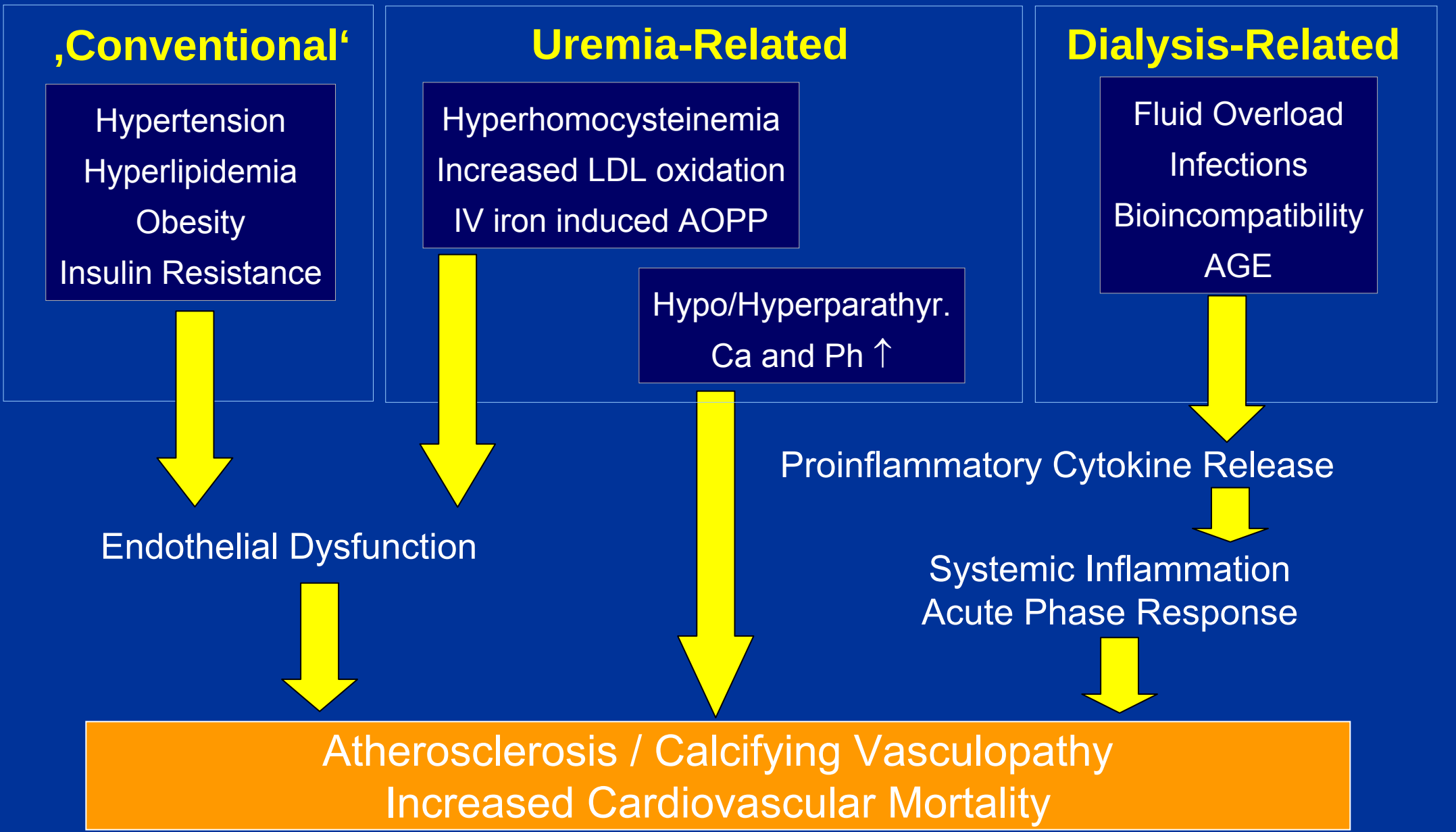
Variables offered to model:

Age, sex, BMI, disease status, smoking habits, CRP, total, LDL, HDL cholesterol, HbA1c, C peptide, Chlamydia IgG, homocysteine

Variables selected:

	Effect	Partial R^2	Total R^2	P value
Homocysteine	positive	0.13	0.13	0.002
Chlamydia IgG	positive	0.05	0.18	0.03
Age	positive	0.07	0.25	0.01
C-Peptide	positive	0.05	0.30	0.05

Cardiovascular Risk Factors in ESRD



Vitamin D Deficiency in CKD

Does it matter ?

Vitamin D Deficiency

Definition

Vitamin D insufficiency: Plasma 25(OH)D 10-30 ng/ml

Vitamin D deficiency: Plasma 25(OH)D < 10 ng/ml

LaClair et al, Am J Kidney Dis 2005, 45, 1026-33

Vitamin D insufficiency: Plasma 25(OH)D 16-30 ng/ml

Vitamin D deficiency: Plasma 25(OH)D < 16 ng/ml

Drueke et al (KDIGO 2006), KI 2006

Renal $1.25(OH)_2D$ Production Is Tightly Regulated, but Can Become Substrate Dependent:

- Hypoparathyroidsim
- Hyperparathyroidism
- Vitamin D deficiency
- Chronic renal failure
- Sarcoidosis

Tissue Specific Micro-Endocrine Systems for Vitamin D

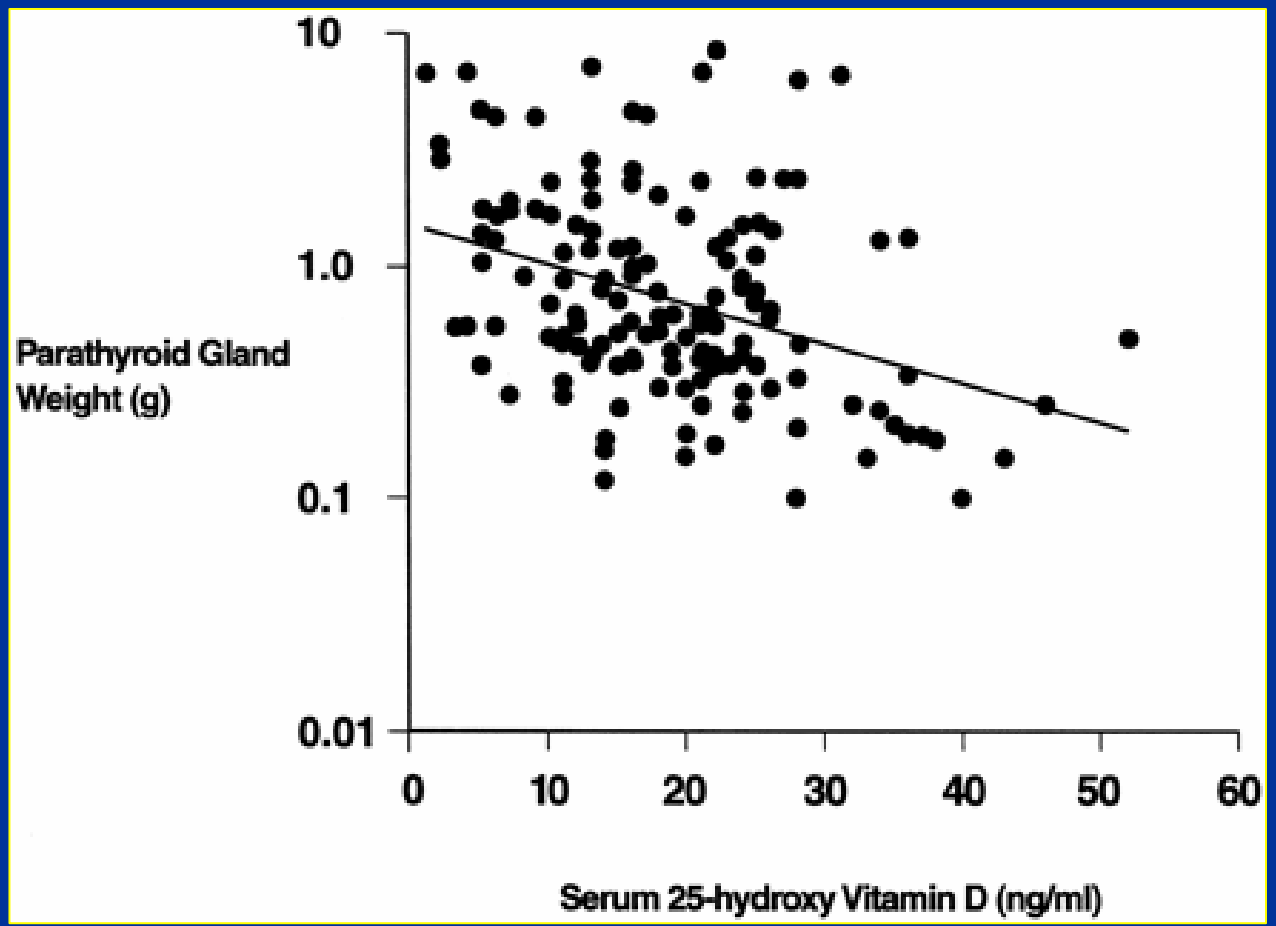
(Extrarenal Production of Calcitriol)

Organs	Diseases
• Immune Cells	Immune Diseases
• Muscles	Weakness
• Bone cells	Osteomalacia
• Vascular myocytes	Cardiovascular disease
• Parathyroid gland	Hyperparathyroidism
• Prostate	Cancer
• Colon	Cancer
• Breast	Cancer
• Others	

PTH levels are inversley correlated with 25(OH)D levels

- Primary hyperparathyroidism
  Rao et al, J Clin Endocrinol Metab 2000, 85, 1054,
- Secondary hyperparathyroidism
  Lemonte et al,J Nephrol 2005,8,96
  Holick AJKD, 2005,6,1119

Effect of 25(OH)-D on Primary Hyperparathyroidism



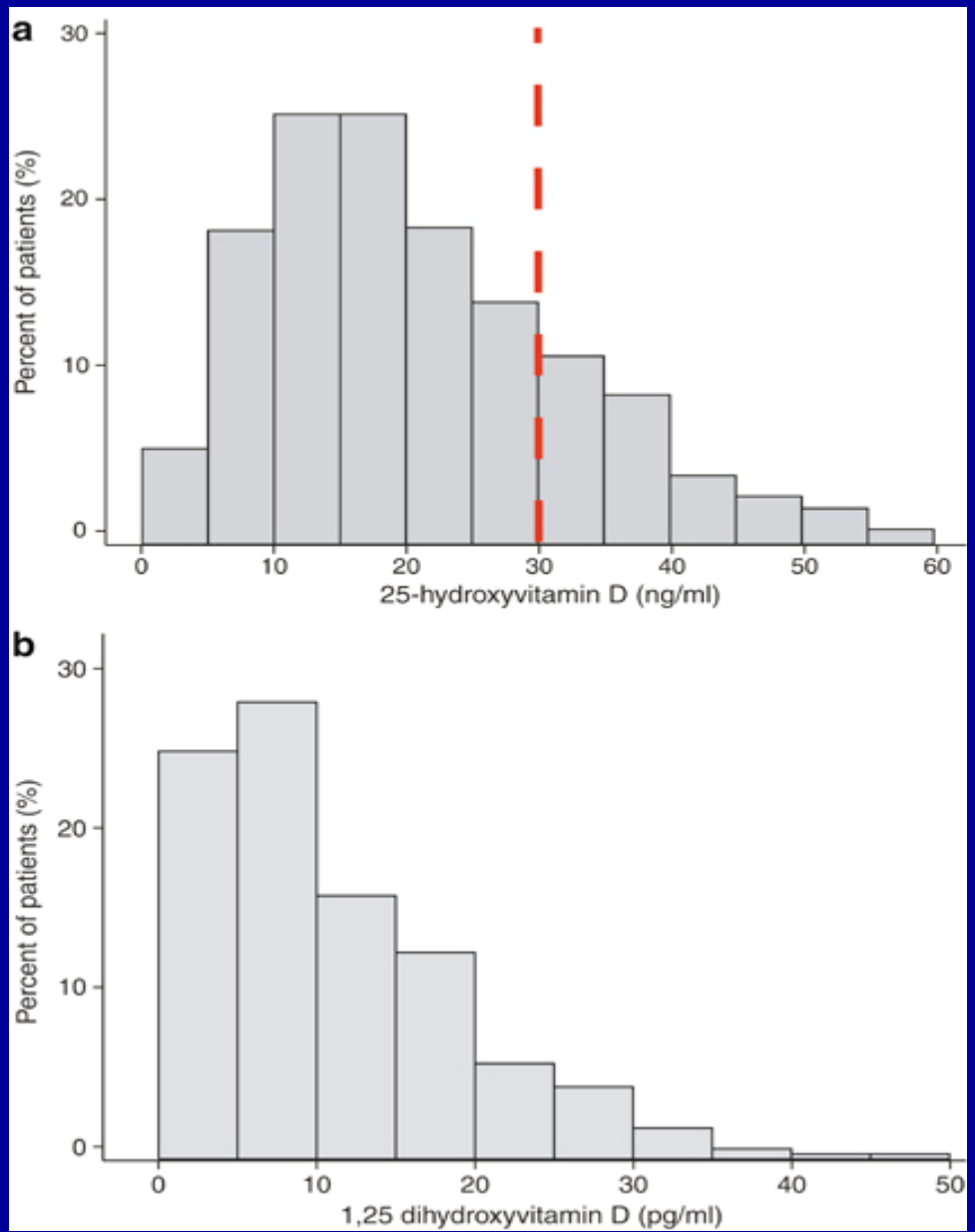
Rao DS et al., J Clin Endocrinol Metab 2000 Mar;85(3):1054-8

Vit.D Status and PTH in Primary Hyperparathyroidism

	25(OH)D (ng/ml)		*p*
	<15	*>15*	
25(OH)D (ng/ml)	9.3 ± 4	24 ± 7	<0.001
1.25$(OH)_2$D (pg/ml)	63 ± 22	61 ± 16	n.s.
p-gland weight (g)	1.1 ± 2.7	0.6 ± 2.6	0.002
iPTH (pg/ml)	172 ± 192	104 ± 71	0.002

Rao et al, J Clin Endocrinol Metab 85, 1054, 2000

Vitamin D levels in Incident Hemodialysis Patients



Wolf et al, Kidney Int 2007

Prevalence of Vitamin D Insufficiency in Dialysis Patients

Number of patients:	119
Age (years)	64 ±14
25(OH)D (ng/ml)	17 ± 7
Sufficient 25(OH)D levels (%)	9
25(OH)D after 50,000 IU D2/month	54 ±16

Saab et al, Nephron Clin Pract 2007, 105, c132-8

Prevalence of Vitamin D Deficiency in CKD

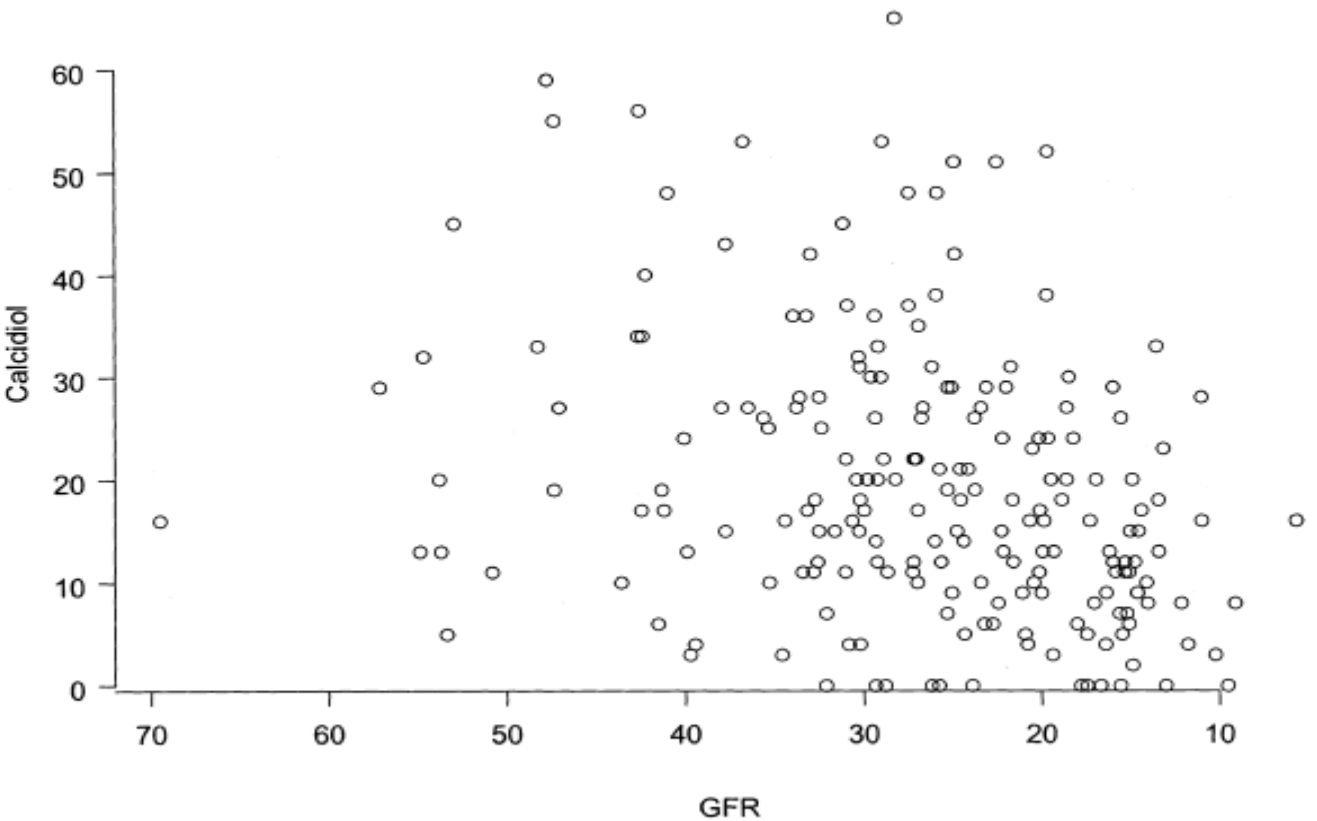
Number of patients:	201
Age (years)	65 ±13
GFR (ml/min x1.73 m²)	27 ±11
25(OH)D (ng/ml)	19 ±14
Sufficient 25(OH)D levels (%)	29

Independent correlations (multivariate analysis)

1. Positive with serum Ca++
2. Negative with serum PTH
3. No correlation with GFR

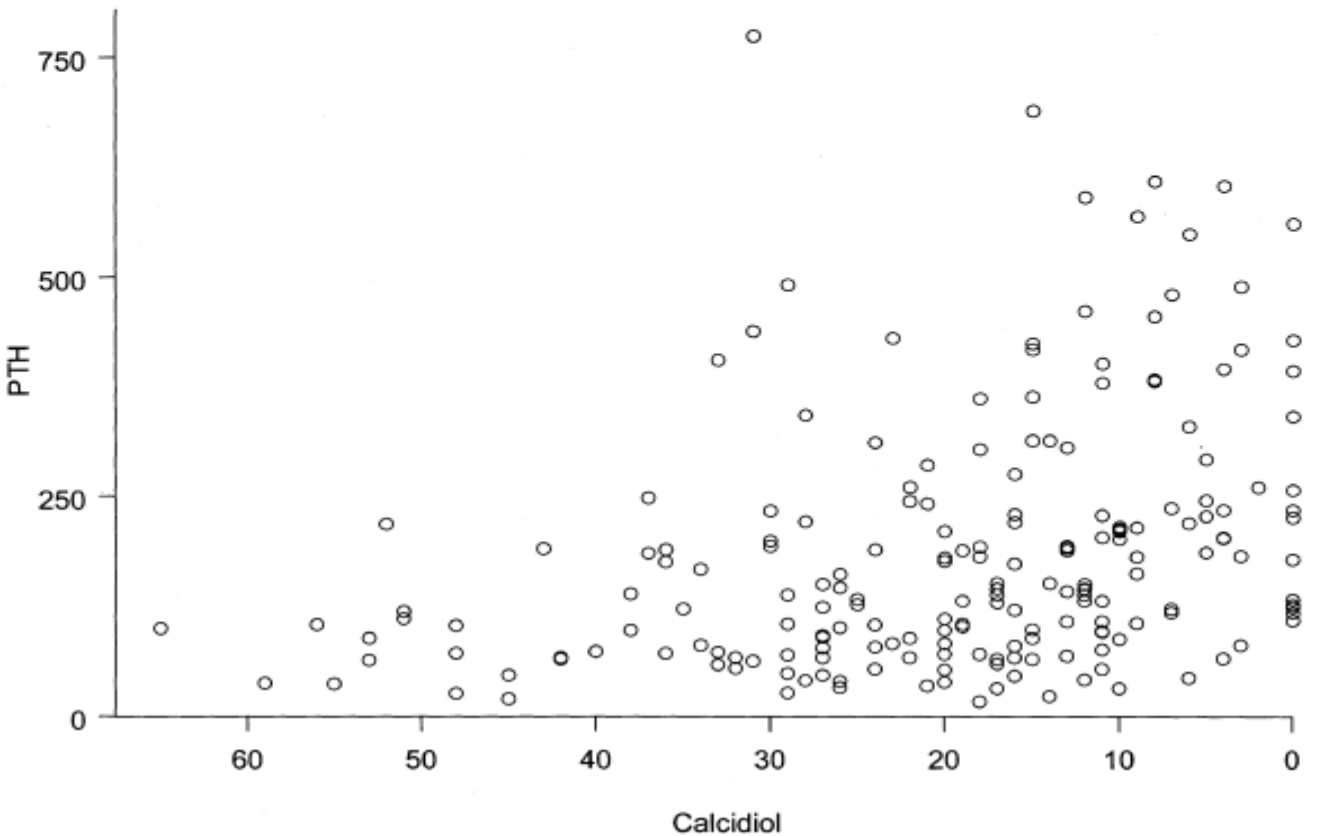
LaClair et al, Am J Kidney Dis 2005, 45, 1026-33

25(OH)D Level versus GFR



LaClair et al, Am J Kidney Dis 2005, 45, 1026-33

PTH Level versus 25(OH)D



LaClair et al, Am J Kidney Dis 2005, 45, 1026-33

Multivariate-Adjusted Odds Ratio of **Early Mortality** according to Vitamin D Levels in Incident Hemodialysis Patients

	Plasma 25(OH)D		
	<10 ng/ml	10-30 ng/ml	>30 ng/ml
All-cause mortality	1.6	1.3	1.0
Cardiovascular mortality	1.6	1.6	1.0

Wolf et al, Kidney Int, August 2007

Prevention and Therapy

Vitamin D_3 Prophylaxis and Treatment for Vitamin D Insufficiency/Deficiency

Health

	Children	Adults
Maintenance prevention	400-1,000 IU/day	800-1,000 IU/day
Treatment	5,000 IU/day 200,000 IU/3 months	15,000 IU/week for 8 weeks

CKD

Maintenance prevention	1,000 IU/day	15,000 IU bolus every 3 months
Treatment	15,000 IU every 2 weeks	15,000 IU every 2 weeks

Vitamin D_3 3 times more efficient than vitamin D_2

Holick NEJM 2007

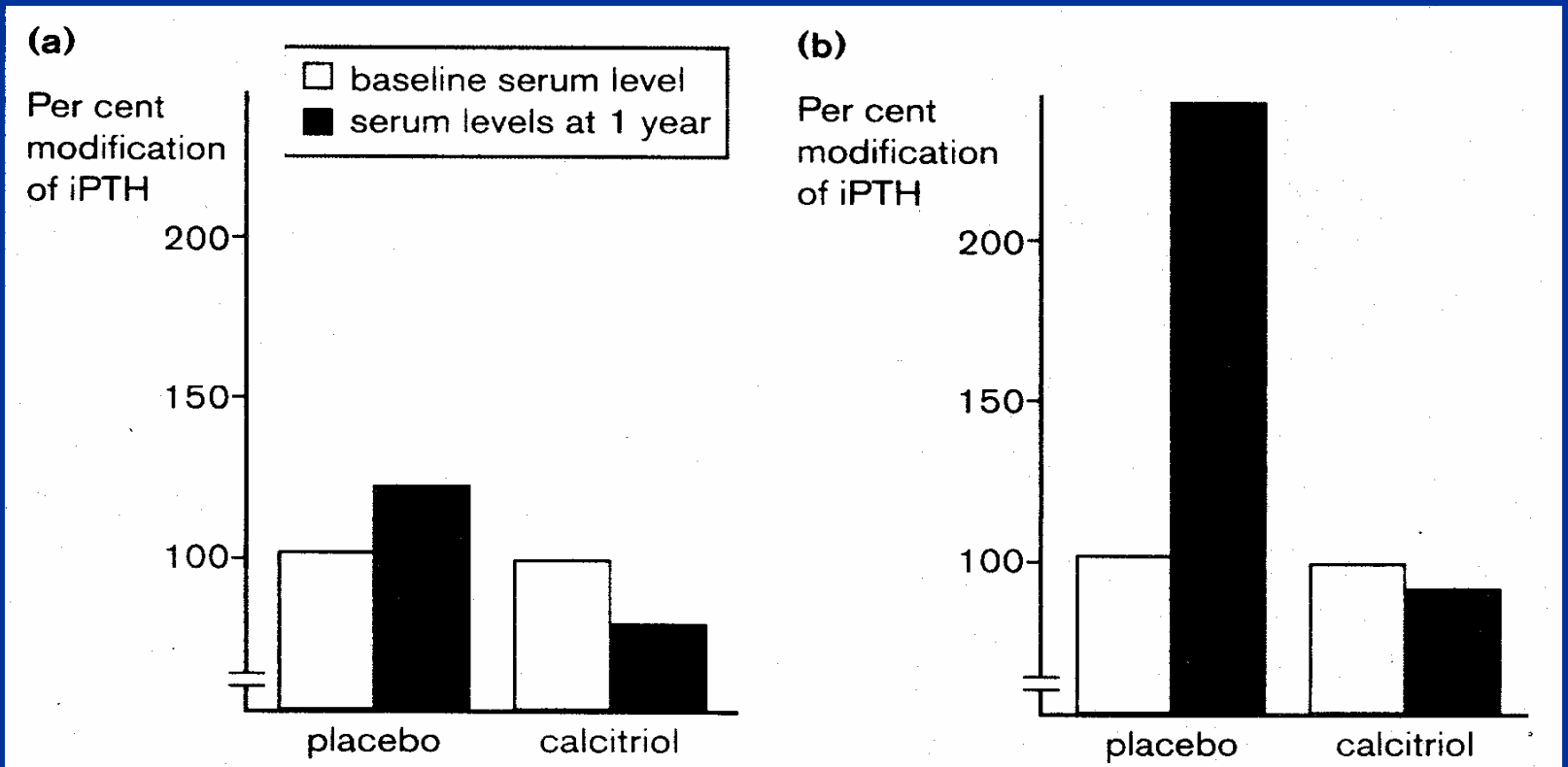
Calcitriol Treatment Recommendations

- Start low-dose daily calcitriol early in CRF (prophylaxis of parathyroid hyperplasia)
- Oral daily calcitriol as effective as and probably safer than . Intermittent (iv or ororal) pulse therapy
- Target PTH: according to renal function,2-times normal in CKD V
- Monitoring policy:
  Check PTH and Ca^{2+} frequently, but avoid frequent dose changes (parathyroid rebound activation)!
  Check compliance!

Prevention of HPT by Calcitriol

Scr < 3 mg/dL

Scr > 3 mg/dL



Ritz et al. NDT 1995, 10:2228

Strategies to Control Serum Calcium and Phosphate

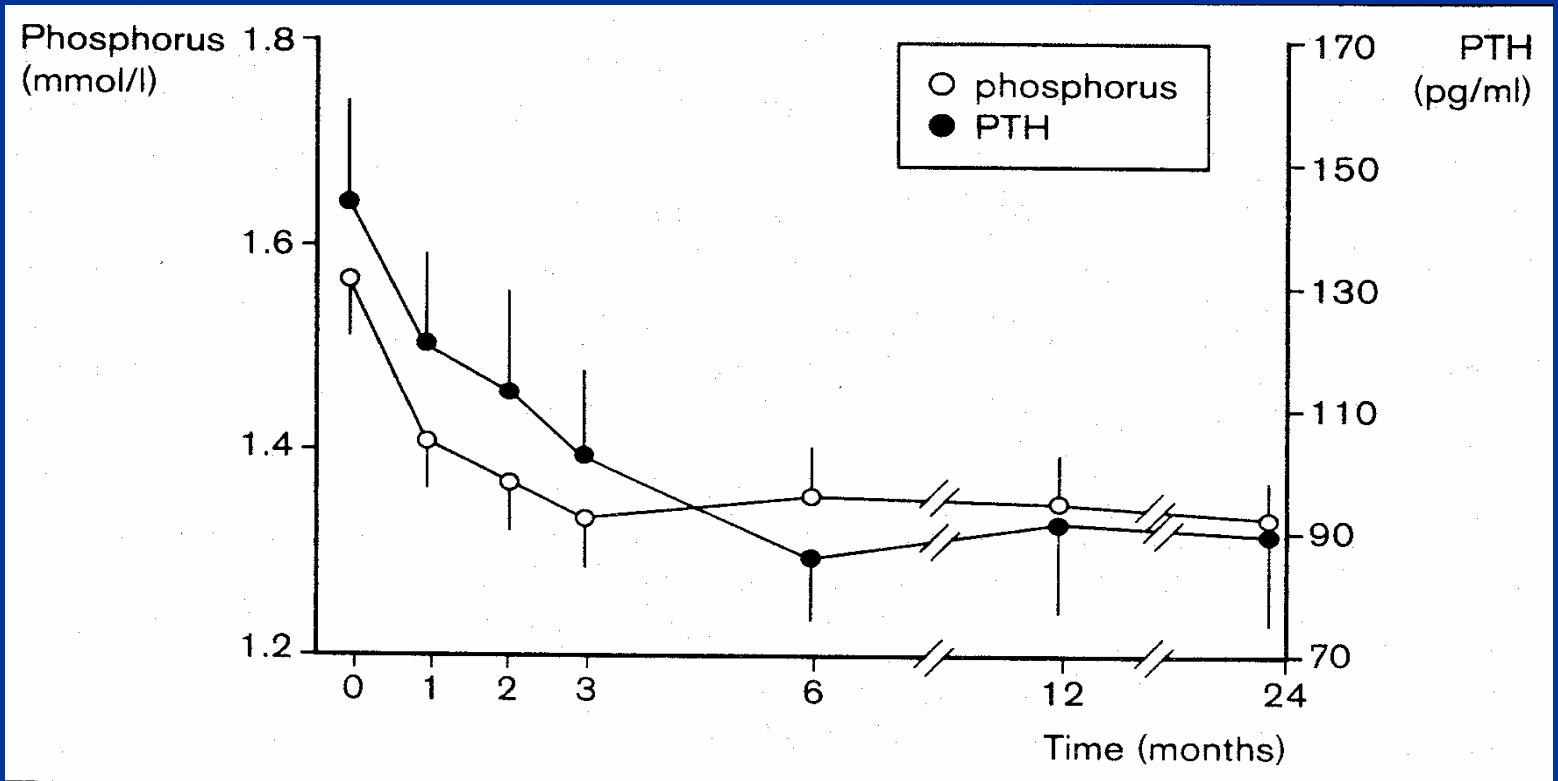
a. Diet: Low phosphate intake

b. Dialysis: Longer duration for hyperphosphatemia
Lower [Ca^{++}] dialysate for hypercalcemia

c. Vitamin D: Reduce intake if hypercalcemia and/or hyperhosphatemia

d. Phosphate binder: Ca-free binder for hypercalcemia

Control of HPT by Low-Phosphorus Diet

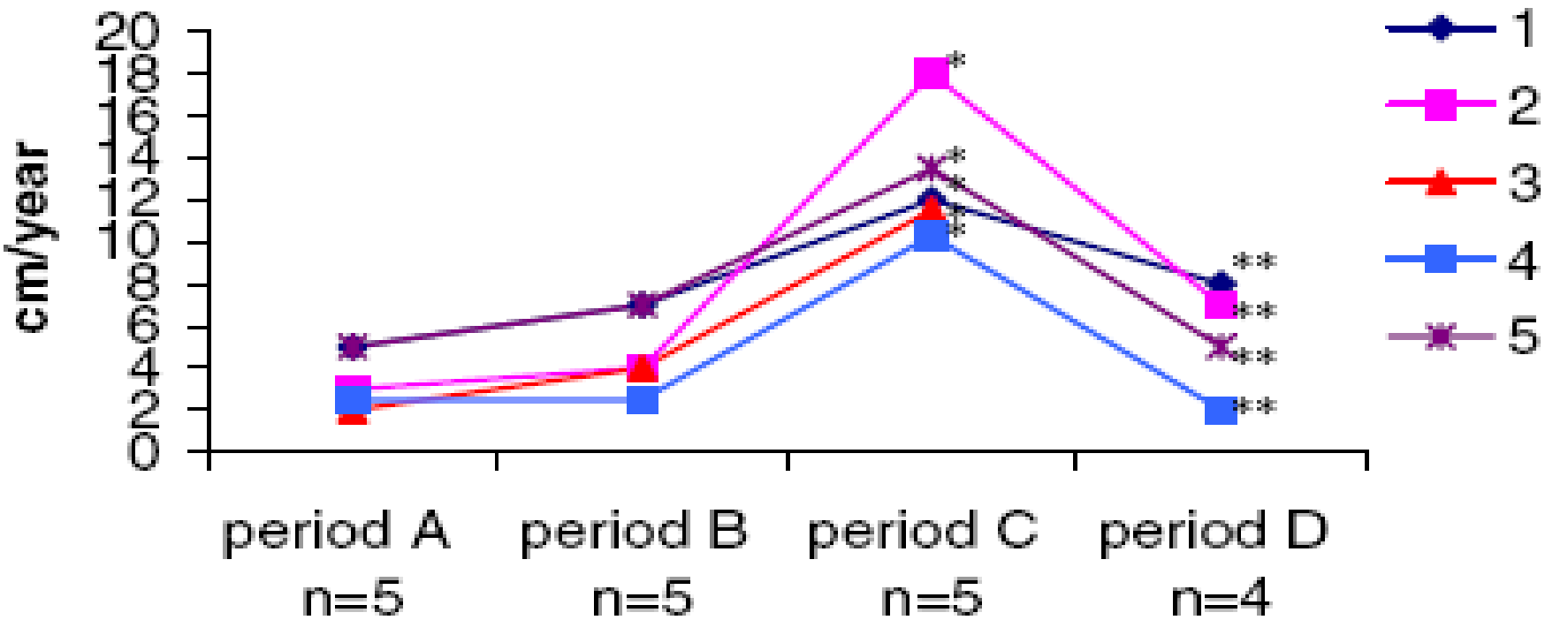


Combe et al. Nephron 1995, 70:287

Phosphate Balance in an Anuric Dialysis Patient

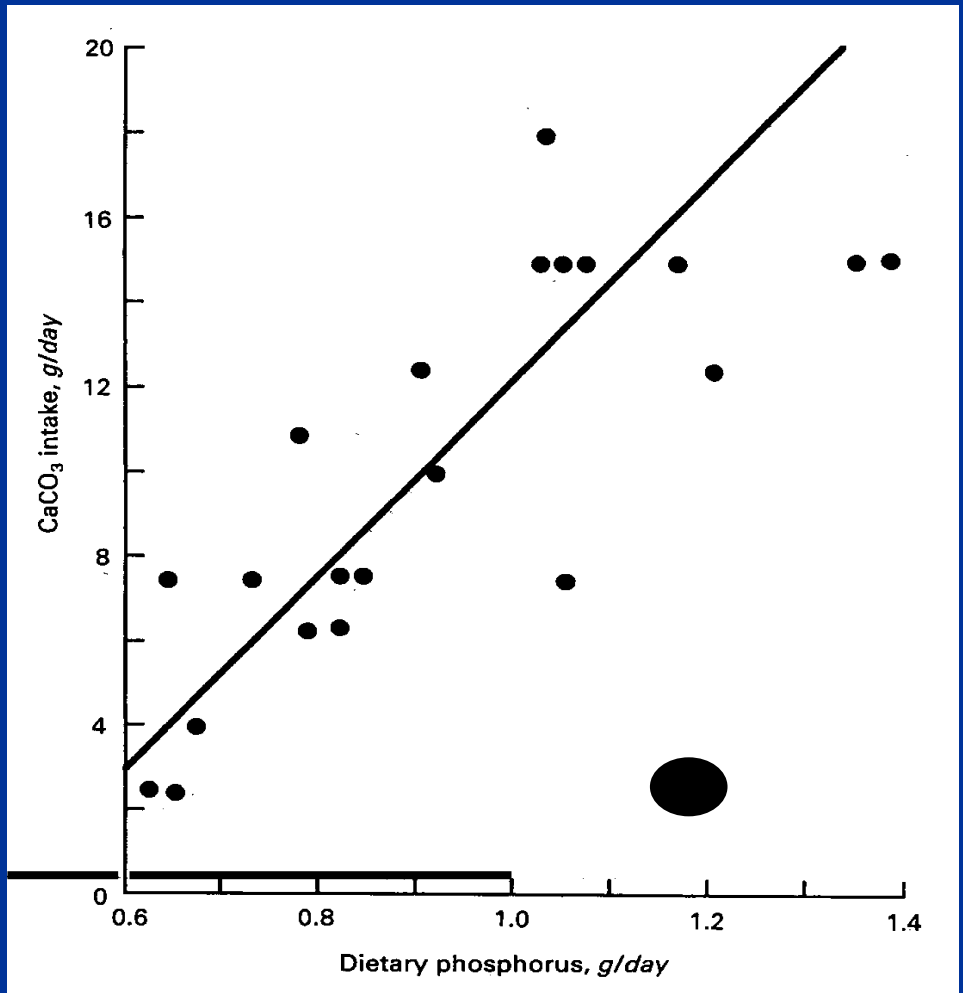
Phosphate intake	1,000 mg/day
Phosphate intestinal absorption	600 mg/day
Phosphate removal by dialysis	2,400 mg/week
Balance	+1,800 mg/week

Improvement of response to GH following dayly dialysis



Fischbach et al ,Ped Neph 2006

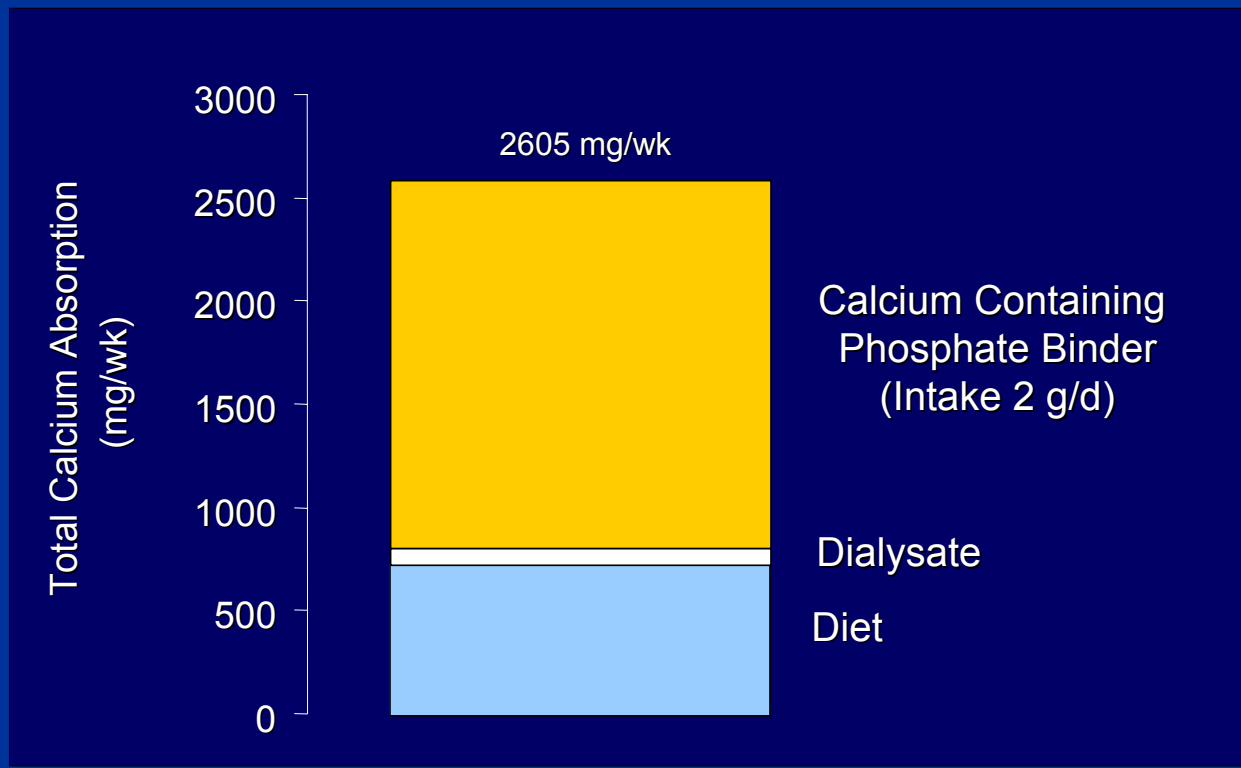
Phosphorus Intake and Calcium Carbonate Requirements



Slatopolsky et al. KI 1989;36:897-903

Sources of Calcium Load in Dialysis Patients

- Dietary calcium
- Dialysate
- Calcium-containing phosphate binders
- Vitamin D therapy (increases Ca absorption)



Bleyer et al. *AJKD* 1999;33:694-701, Hsu *AJKD* 1997;29:641-649

ESRD Patients on Calcium Binders: Where Does Excess Calcium Go?

Weekly Intake
13.7 g

↓

Absorbed Calcium
>2.6 g

⇢

RATE LIMITED

Excretion
1 g

Limited routes

Regulated load
capacity

Tissue

↑

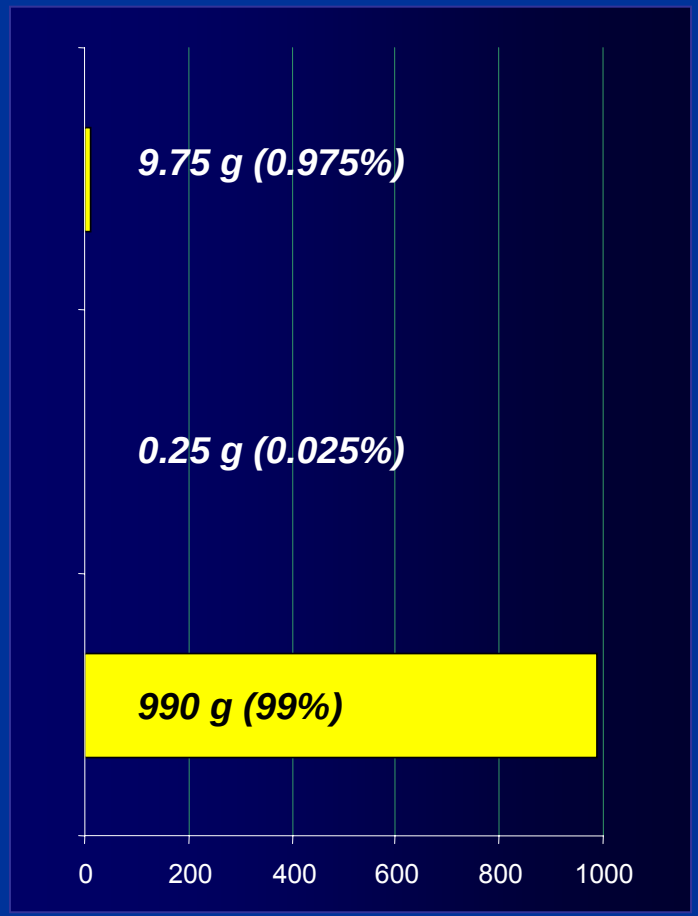
Plasma

⇣

RATE LIMITED

Bone

Low-turnover bone disease



Total body calcium reservoir
1000 g (normal)

Alternative: Non-Ca Containing Phosphate Binders

1. Sevelamer

   Adverse event: Gastrointestinal discomfort

   Pleiotropic effects: Correction of lipid abnormalities

2. Lantanum carbonate:

   Adverse event: Tissue accumulation of Lantanum

Calcimimetics

- Act as allosteric modulators of the calcium-sensing receptor
- Decrease PTH, Ca and P
- Lower cardiovascular risk profile
  - by lowering PTH?
  - by direct effects on vessels and adipocytes?

Treatment Guidelines

Serum Ca	Serum P_i	Serum PTH	
Normal or low	High	> 350 pg/ml	Reduce dietary P_i and begin P_i binders ($CaCO_3$) Begin daily calcitriol when Pi normalized
High	Normal or low	< 150 pg/ml	Stop Ca-containing Pi binders Stop Calcitriol Use low-Ca dialysate Consider Renagel
Normal or high	High	> 500 pg/ml	Hold calcitriol Scan for PT adenoma Increase Pi binders: Ca acetate, consider Renagel, temporary aluminium hydroxide Consider calcimimetics Consider parathyroidectomy