MINERAL METABOLISM IN CKD EXCITING SCIENCE AND CHANGING PRIORITIES

Leading with Innovation
Serving with Compassion

ST. MICHAEL'S HOSPITAL

A teaching hospital affiliated with the University of Toronto

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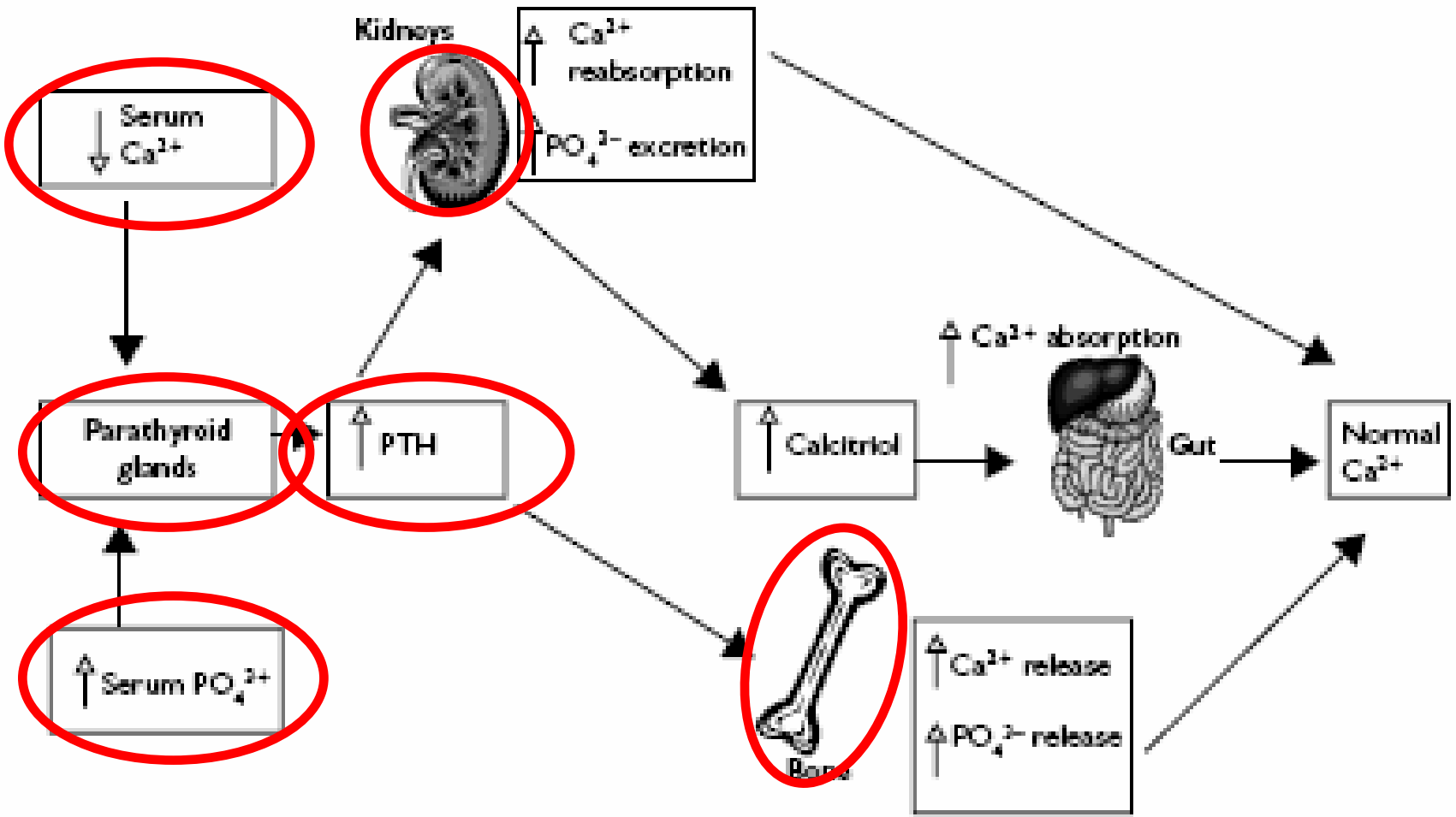
BC Nephrology DAYS 2007

OBJECTIVES

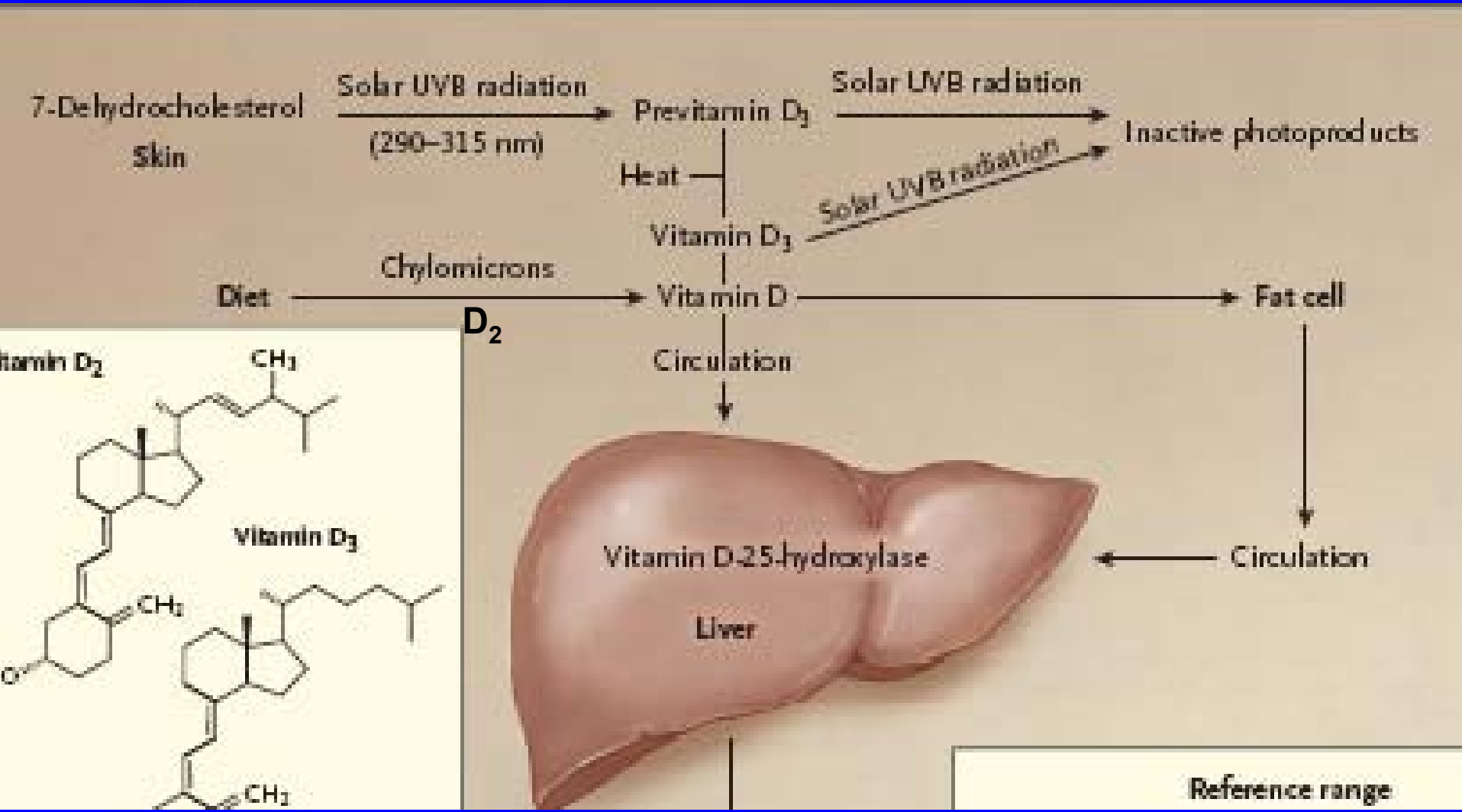
- Review the normal physiology and pathophysiology of Ca PO_4 and PTH regulation in CKD.
- Illustrate the clinical importance of disturbances in Mineral Metabolism in CKD.
- Draw your attention to the basic science advances in this area.
- Suggest some management strategies for these problems.
- Indicate the remaining knowledge gaps.

Normal Mineral Metabolism Physiology

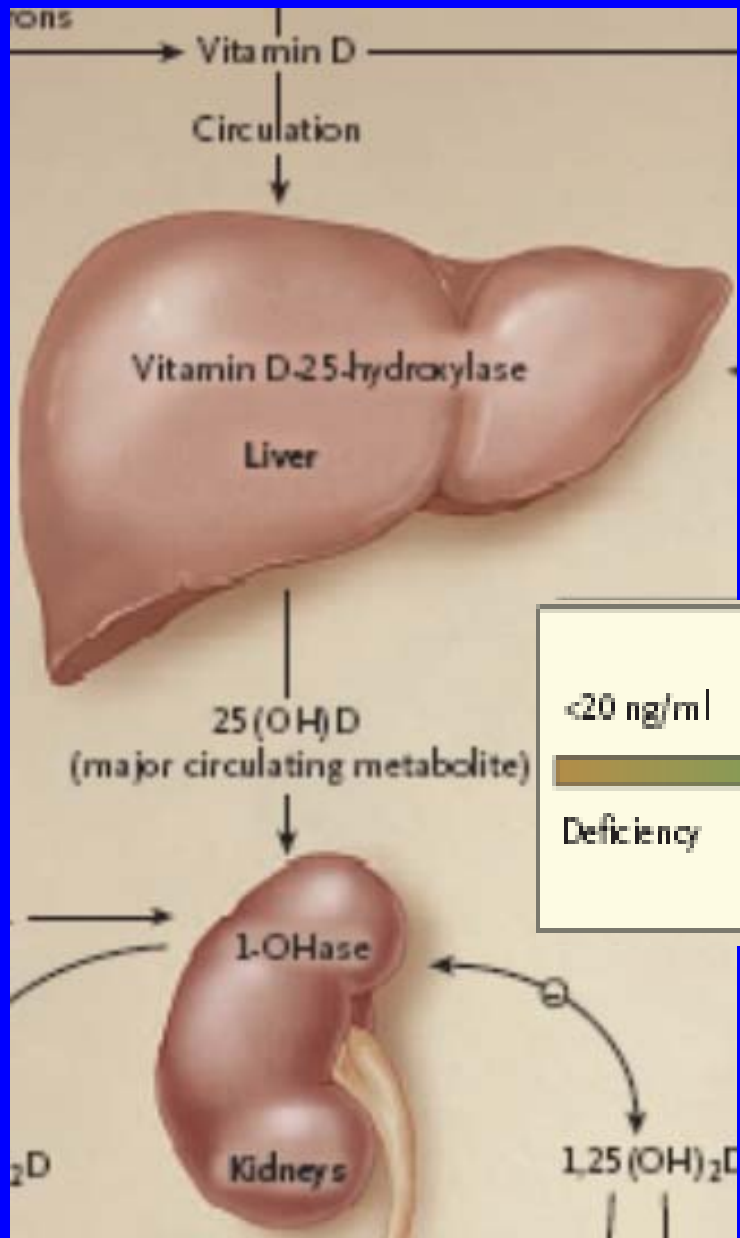


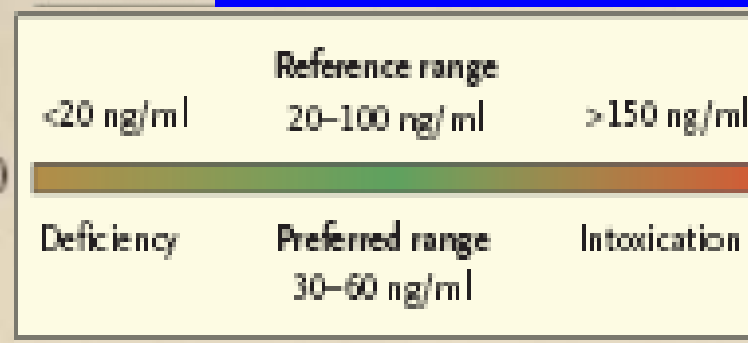
Health Technology Assessment 2007; Vol. 11: No. 18

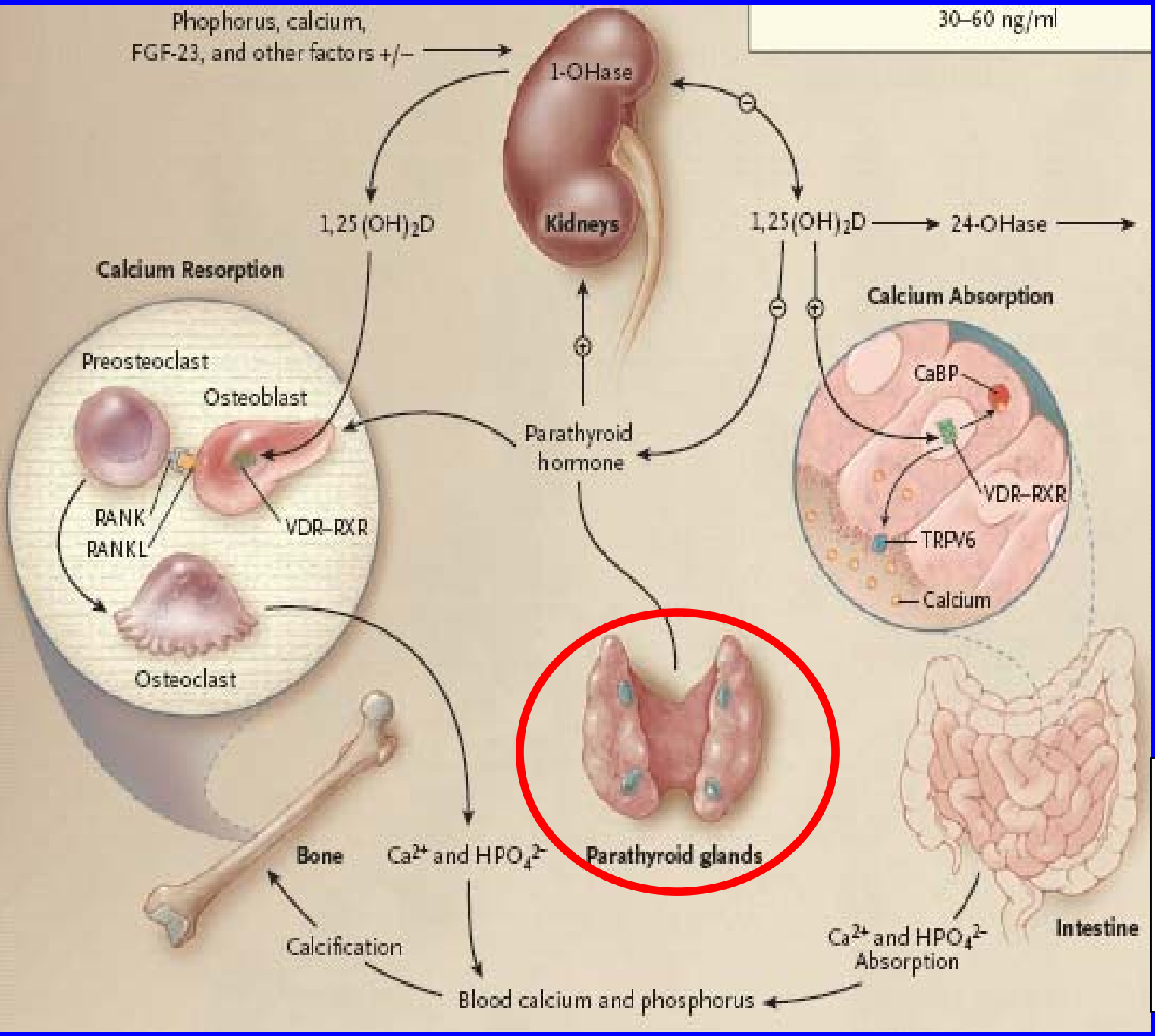
Vitamin D


7-Dehydrocholesterol
Skin
Solar UVB radiation
(290–315 nm)
Previtamin D_3
Heat
Solar UVB radiation
Inactive photoproducts
Solar UVB radiation
Vitamin D_3
Chylomicrons
Diet
Vitamin D
D_2
Fat cell
Circulation
Vitamin D-25-hydroxylase
Liver
Circulation
Reference range
Vitamin D_2
Vitamin D_3
CH_3
CH_2
CH_3

VITAMIN $D_3 \rightarrow$25 OH VITAMIN D$\rightarrow$1,25 DOH VITAMIN D

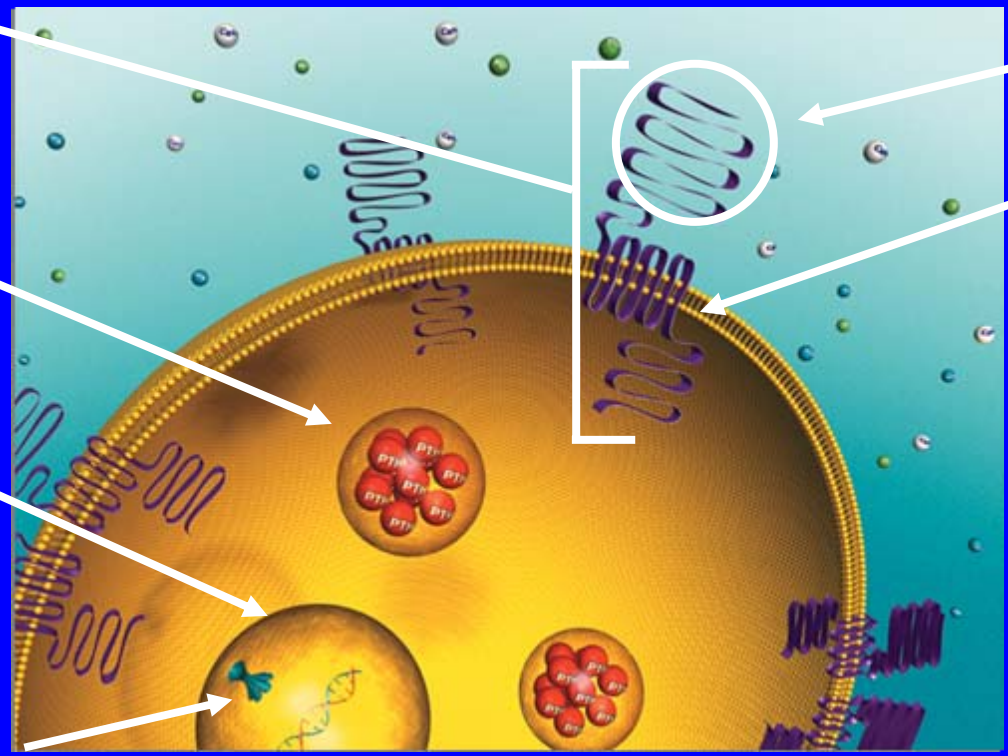






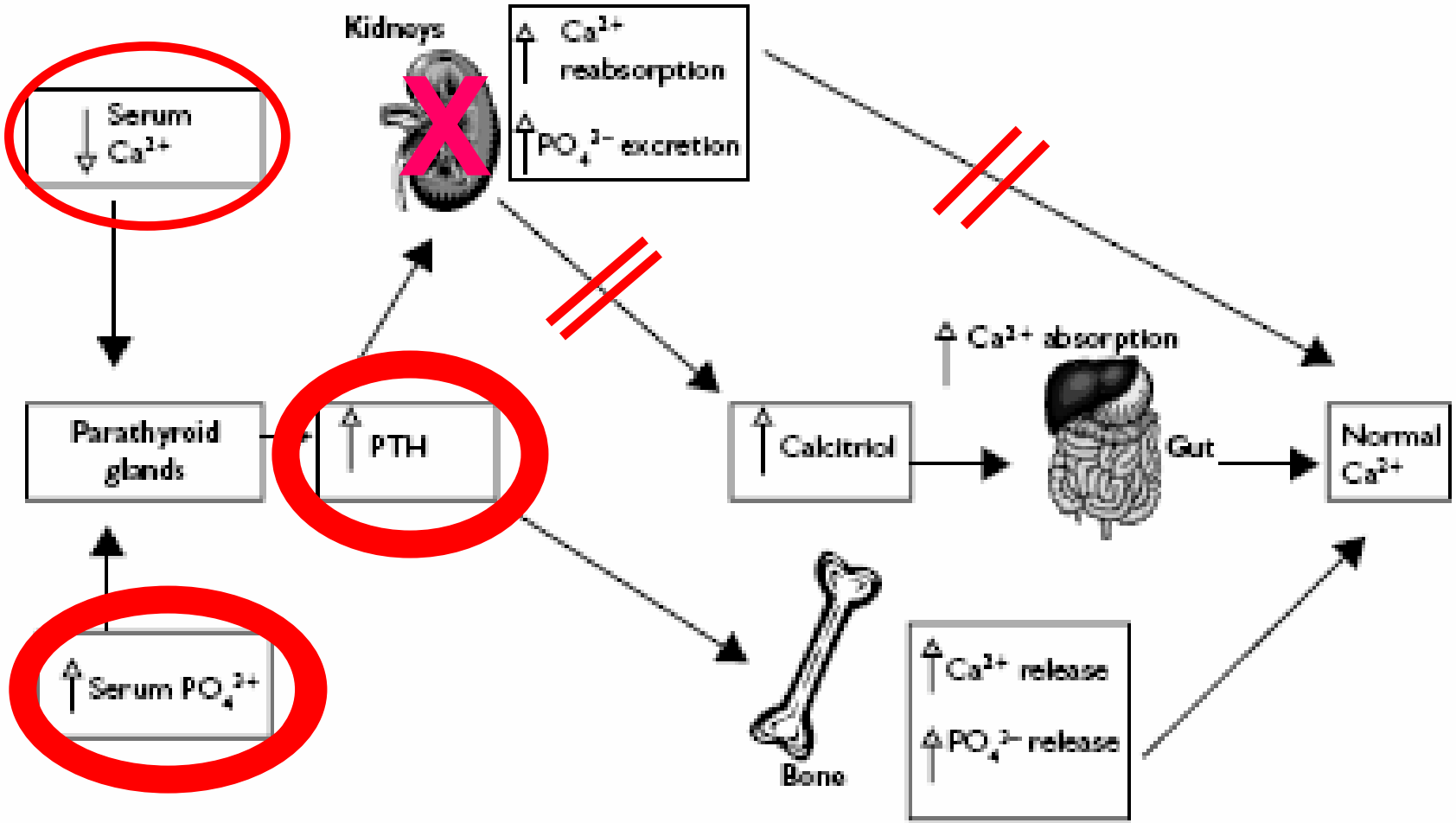
Without 1,25OH vit D 10-15% Ca and 60% PO_4 absorbed
↑to 30-40% Ca & ↑80% PO_4 With ↑1,25 OH vitD

Parathyroid Gland Calcium Regulation and the Calcium-Sensing Receptor



Adapted from Goodman WG. *Kidney Int* 2001;59:1187-1201.

Mineral Metabolism in CKD



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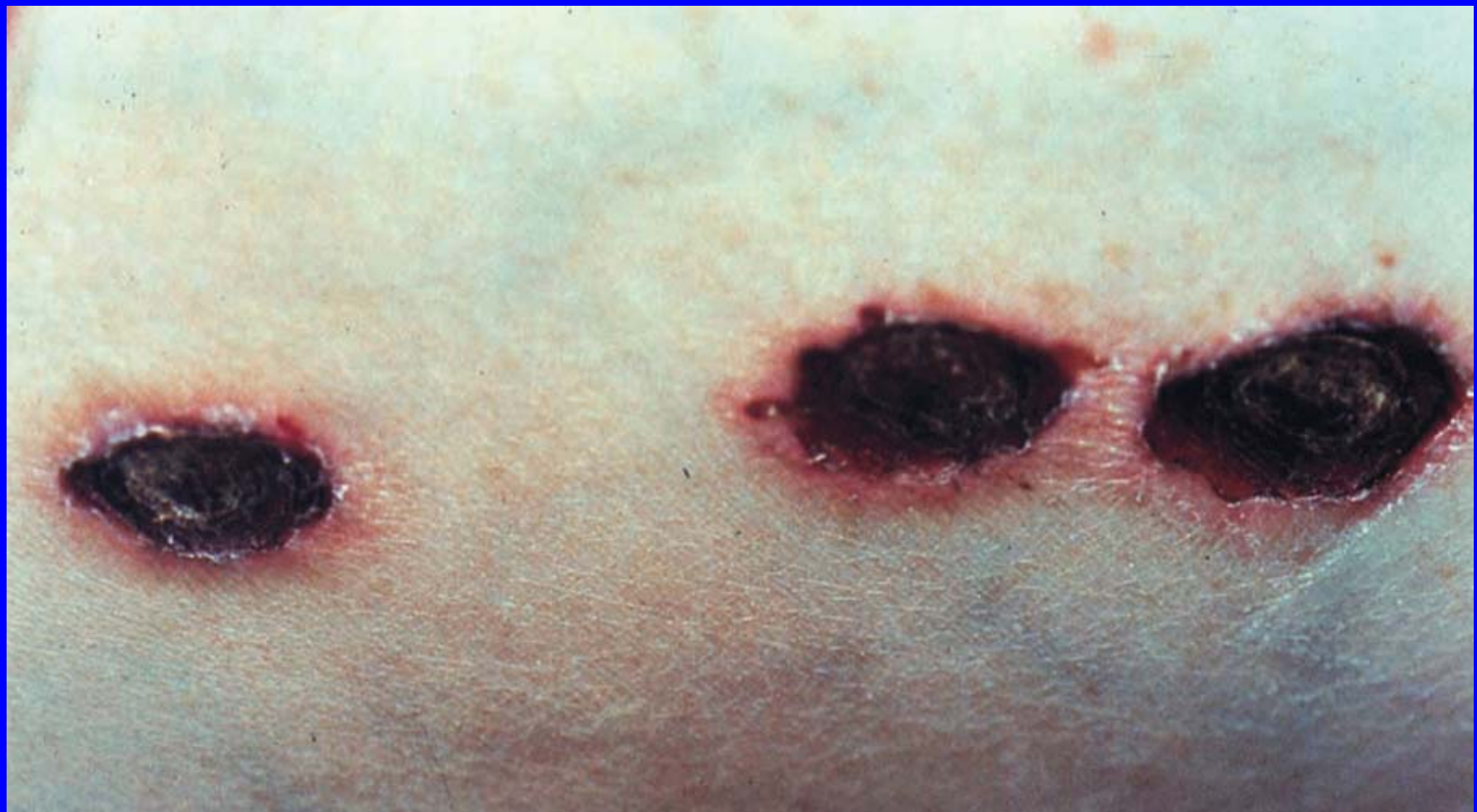
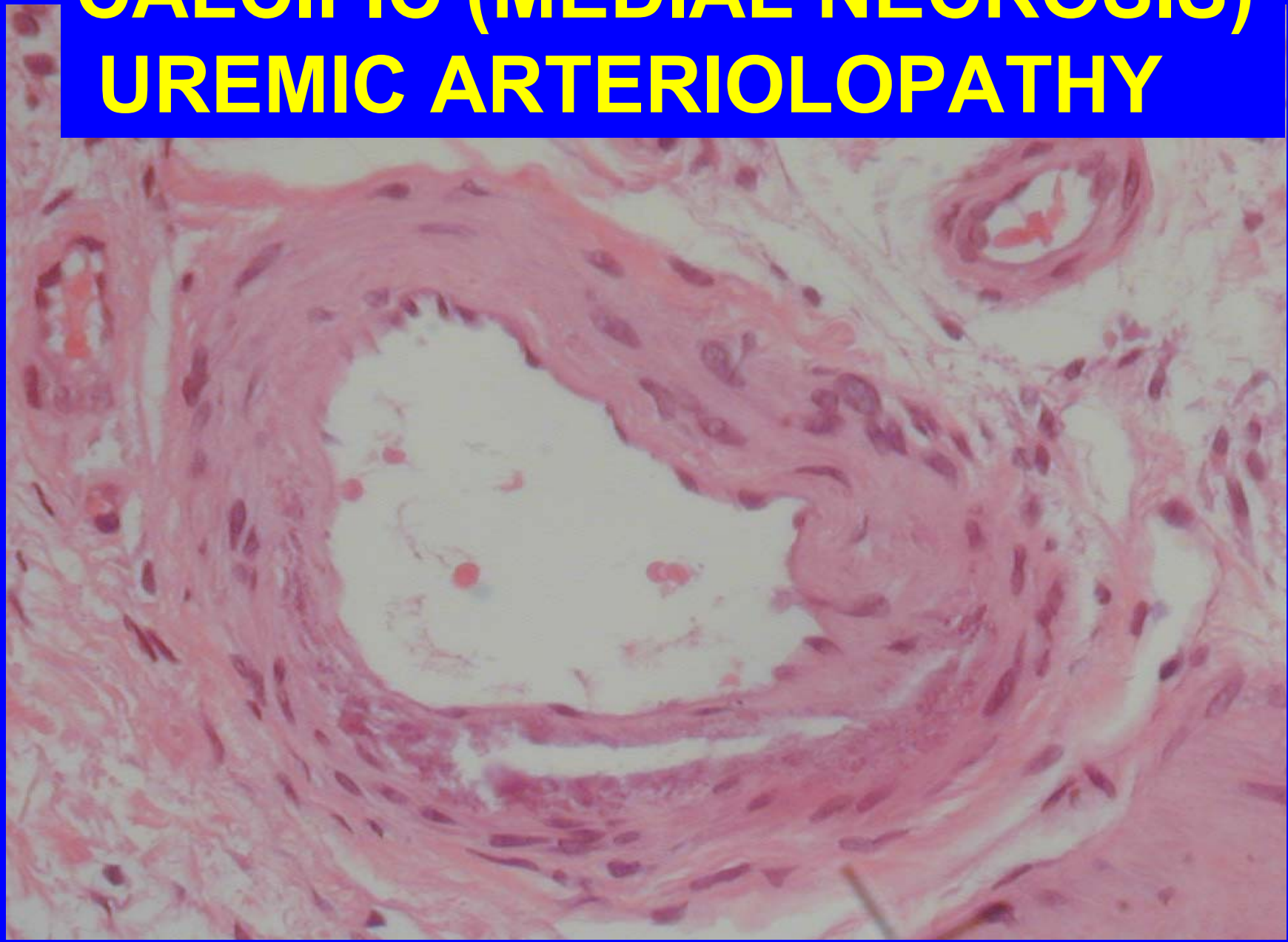
CLASSIC APPEARANCE
CALCPHYLAXIS
Calcific uremic arteriolopathy



CALCIFIC (MEDIAL NECROSIS) UREMIC ARTERIOLOPATHY



Calcific Uremic Arteriolopathy

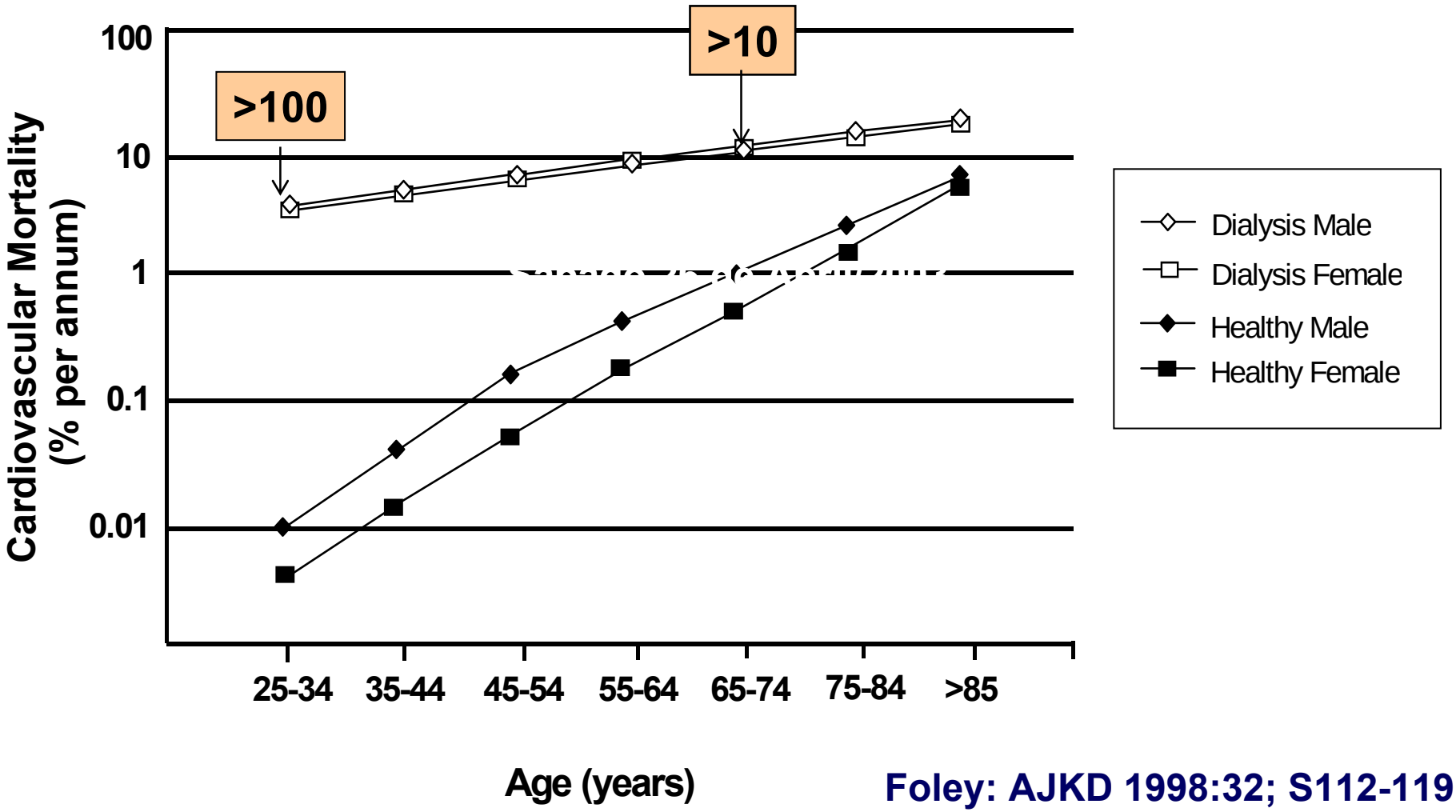
- Was a rare condition 1 in 30 yrs
- Becoming more prevalent 6 in past 5 yrs
- Probably related to changes in the standards of dialysis practice.

Changes in Standards of Practice

- Avoid Aluminum
- Calcium Based PO_4 Binders
- Focus on the Bones and PTH
- Vitamin D Analogues

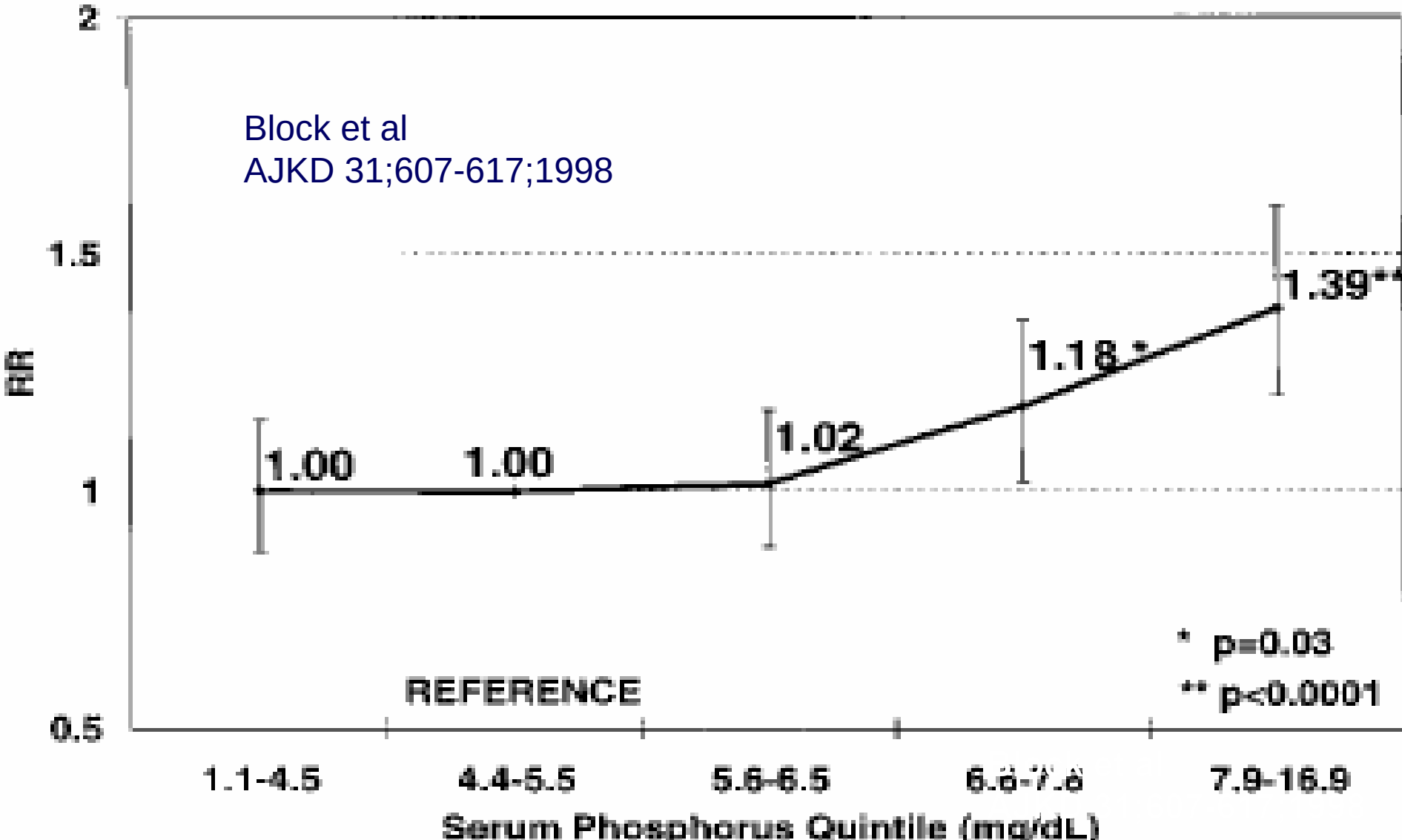
Major increase in incidence focused our attention on the impact of our changes in practice from the bones to the blood vessels

CARDIOVASCULAR MORTALITY IN DIALYSIS



Foley: AJKD 1998:32; S112-119

Mortality Risk Serum PO_4



Phosphate Regulation of Vascular Smooth Muscle Cell Calcification

Shuichi Jono, Marc D. McKee, Charles E. Murry, Atsushi Shioi, Yoshiki Nishizawa, Katsuhito Mori, Hirotoshi Morii, Cecilia M. Giachelli

Vascular SMC cultured in high PO4 medium

PO_4 brings about change in the phenotype of smooth muscle cells, losing SMC features and gaining BONE features.

CIRCULATION RES,1-8: Sept 29, 2000

Phosphate Regulation of Vascular Smooth Muscle Cell Calcification

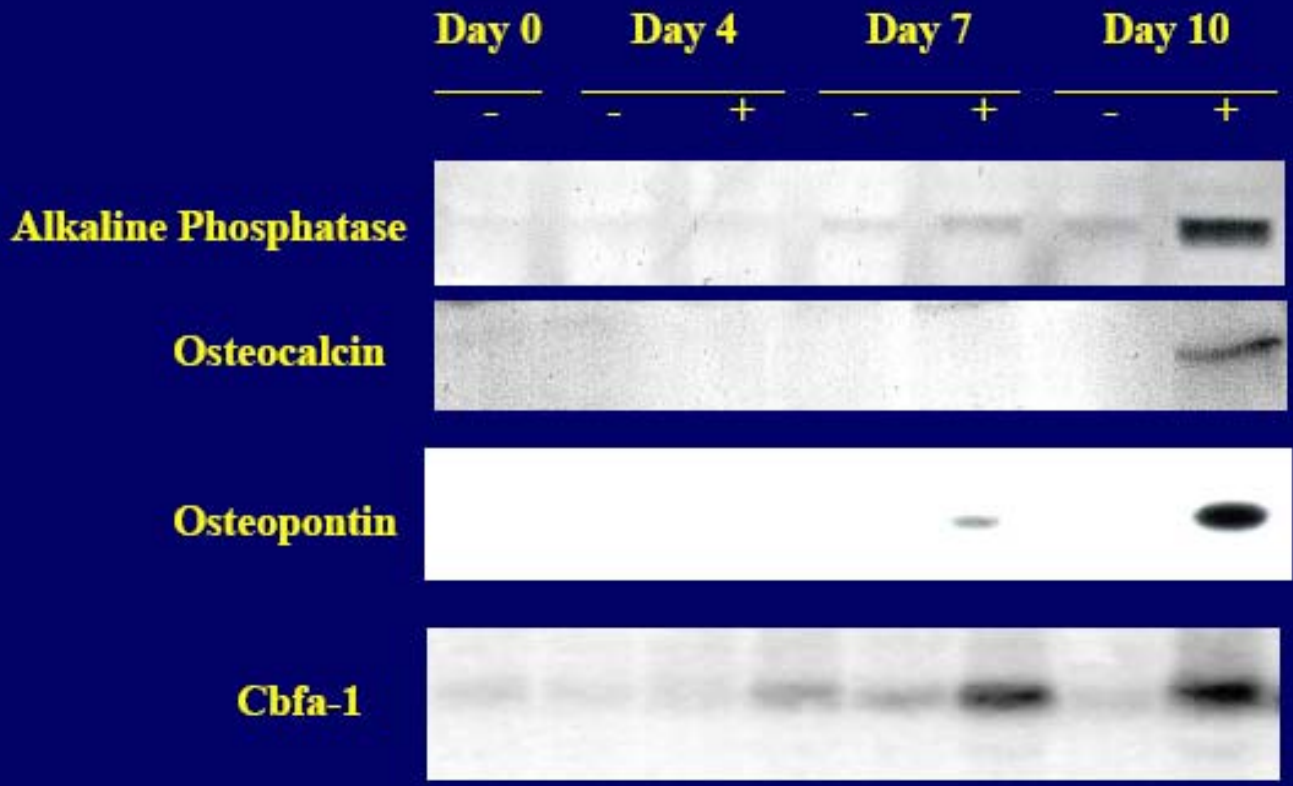
Shuichi Jono, Marc D. McKee, Charles E. Murry, Atsushi Shioi, Yoshiki Nishizawa, Katsuhito Mori, Hirotoshi Morii, Cecilia M. Giachelli

HSMC in ↑ PO_4 (>1.4 mM) medium:

- ↑ Mineral deposition (dose dependant)
- Enhanced expression of osteoblastic markers Osteocalcin, CBFA-1
- Mediated via Na dependant PO_4 cotransporter
- Inhibitor of NPC inhibited above effects of ↑ PO_4

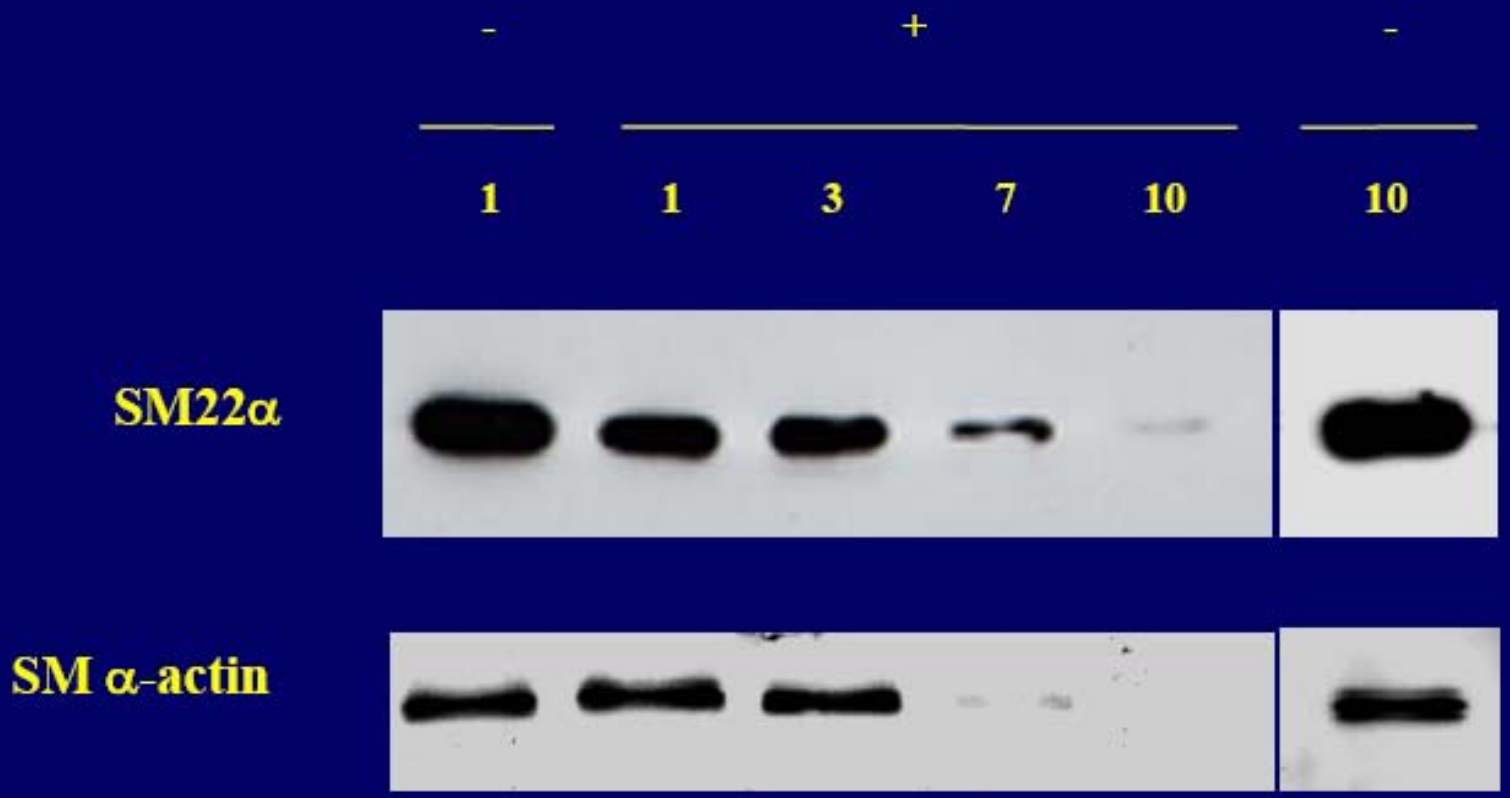
CIRCULATION RES,1-8: Sept 29, 2000

Calcifying SMCs gain an osteogenic phenotype in vitro



Steitz et al. Circ Res 2002

Calcifying SMCs lose smooth muscle markers in vitro



Steitz et al, Circ Res 2002

Calciphylaxis Is Associated With Hyperphosphatemia and Increased Osteopontin Expression by Vascular Smooth Muscle Cells

Sadiq Ahmed, MD, Kalisha D. O'Neill, BS, Antoinette F. Hood, MD, Andrew P. Evan, PhD, and Sharon M. Moe, MD

American Journal of Kidney Diseases, Vol 37, No 6 (June), 2001: pp 1267-1276

CASE CONTROLLED STUDY

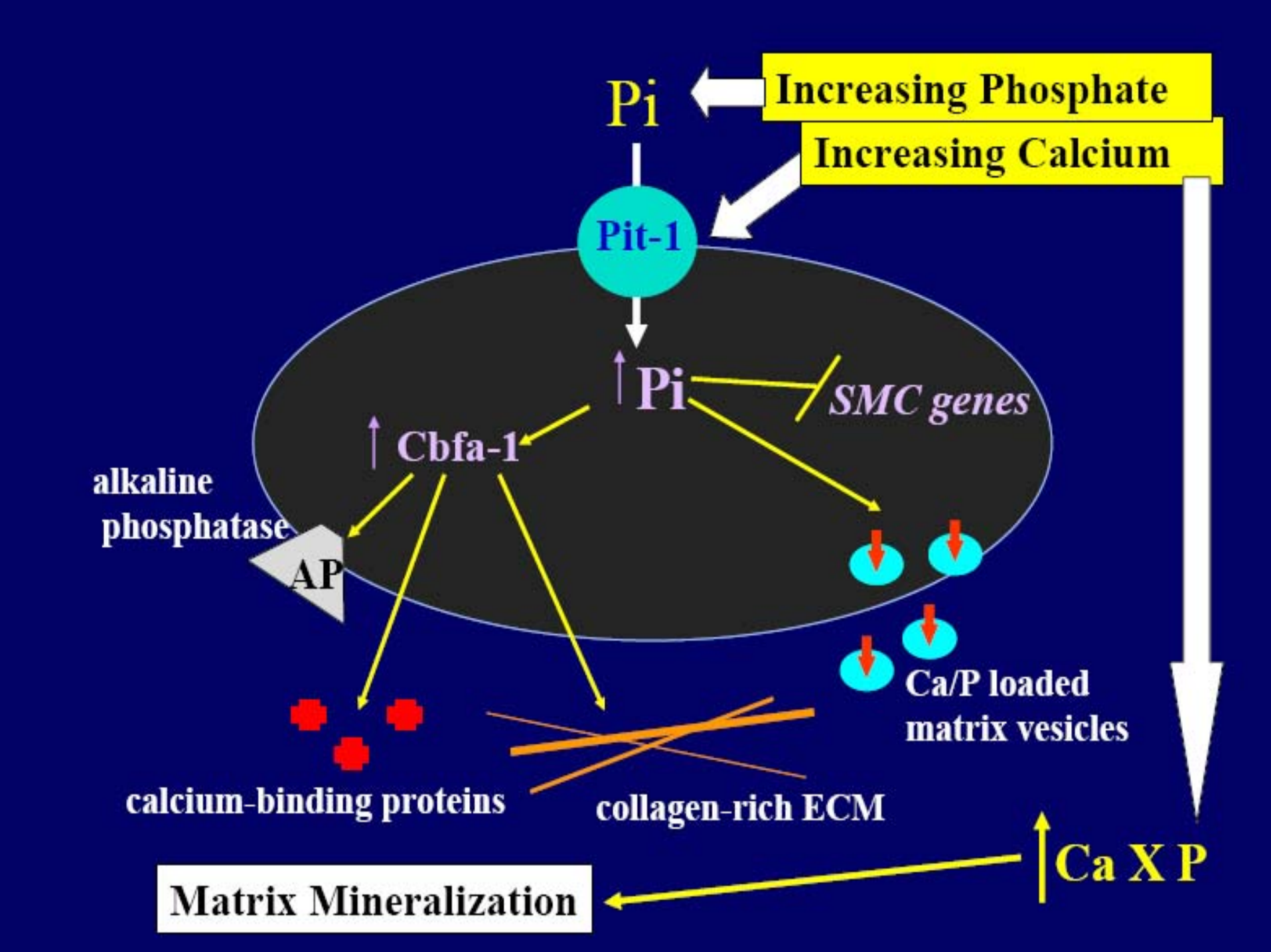
10 CASES DIAGNOSED BY SKIN BIOPSY
Vs
108 chronic hemodialysis patients

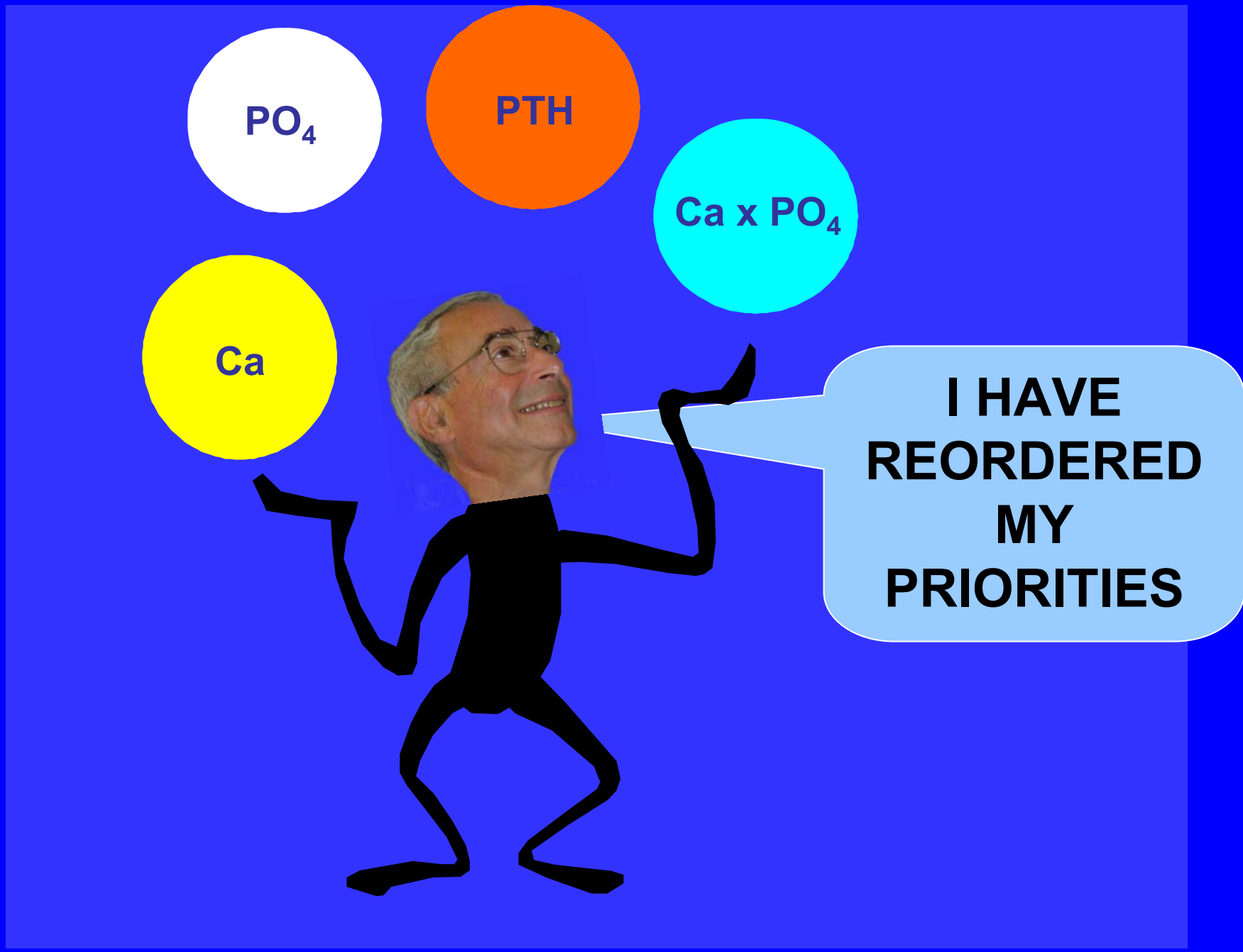
Does Ca play a role in the Vascular Calcification Process?

Kidney International, Vol. 66 (2004), pp. 2293–2299

Elevated extracellular calcium levels induce smooth muscle cell matrix mineralization in vitro[1]

HSUEH YANG, GABRIELLE CURINGA, and CECILIA M. GIACHELLI


Pi
Increasing Phosphate
Increasing Calcium
Pit-1
Pi
SMC genes
Cbfa-1
alkaline phosphatase
AP
Ca/P loaded matrix vesicles
calcium-binding proteins
collagen-rich ECM
Ca X P
Matrix Mineralization


PO_4
PTH
Ca x PO_4
Ca
I HAVE REORDERED MY PRIORITIES

Kidney International, Vol. 63 (2003), pp. 1003–1011

Uremia induces the osteoblast differentiation factor Cbfa1 in human blood vessels

SHARON M. MOE, DANXIA DUAN, BRIAN P. DOEHLE, KALISHA D. O'NEILL, and NEAL X. CHEN

Bovine vascular SMC
Incubated with 10% normal or uremic serum

High glucose increases the expression of Cbfa1 and BMP-2 and enhances the calcification of vascular smooth muscle cells

Neal X. Chen[1], Danxia Duan[1], Kalisha D. O'Neill[1] and Sharon M. Moe[1,2]

Inferior epigastric arteries at time of renal transplant

Diabetics had :

increased calcification

increased expression of bone matrix proteins:

osteopontin, type I collagen,

bone sialoprotein, alkaline phosphatase

BVSMC cultured in high glucose medium

Enhanced calcification (time dependant)

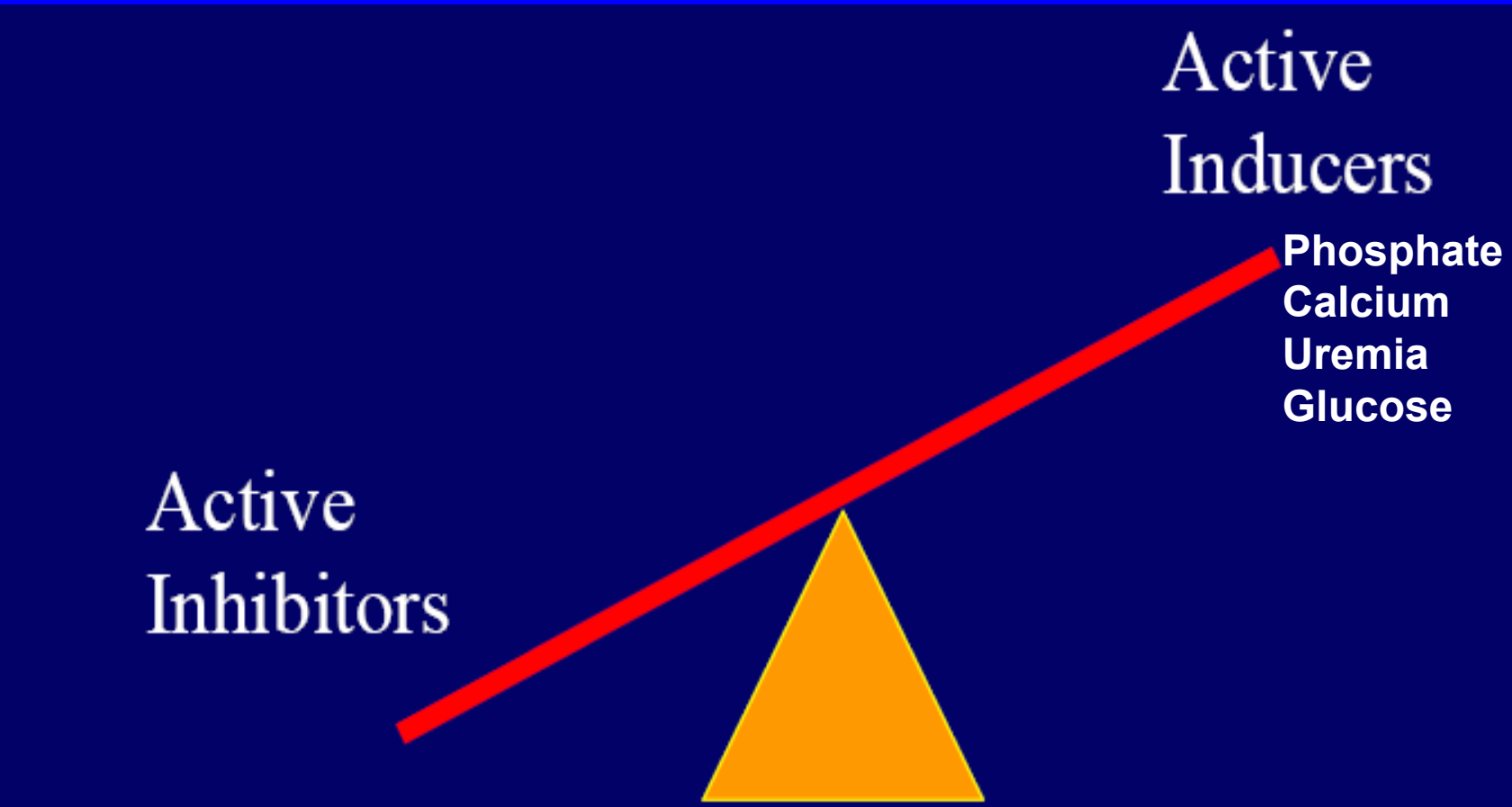
↑expression of osteoblast transcription factor Cbfa 1and osteocalcin

↑secretion of bone morphogenic protein 2

NDT 21: 3435-3442 2006

NORMAL VESSELS DON'T MINERALIZE

Despite Ca x PO4 well above solubility product

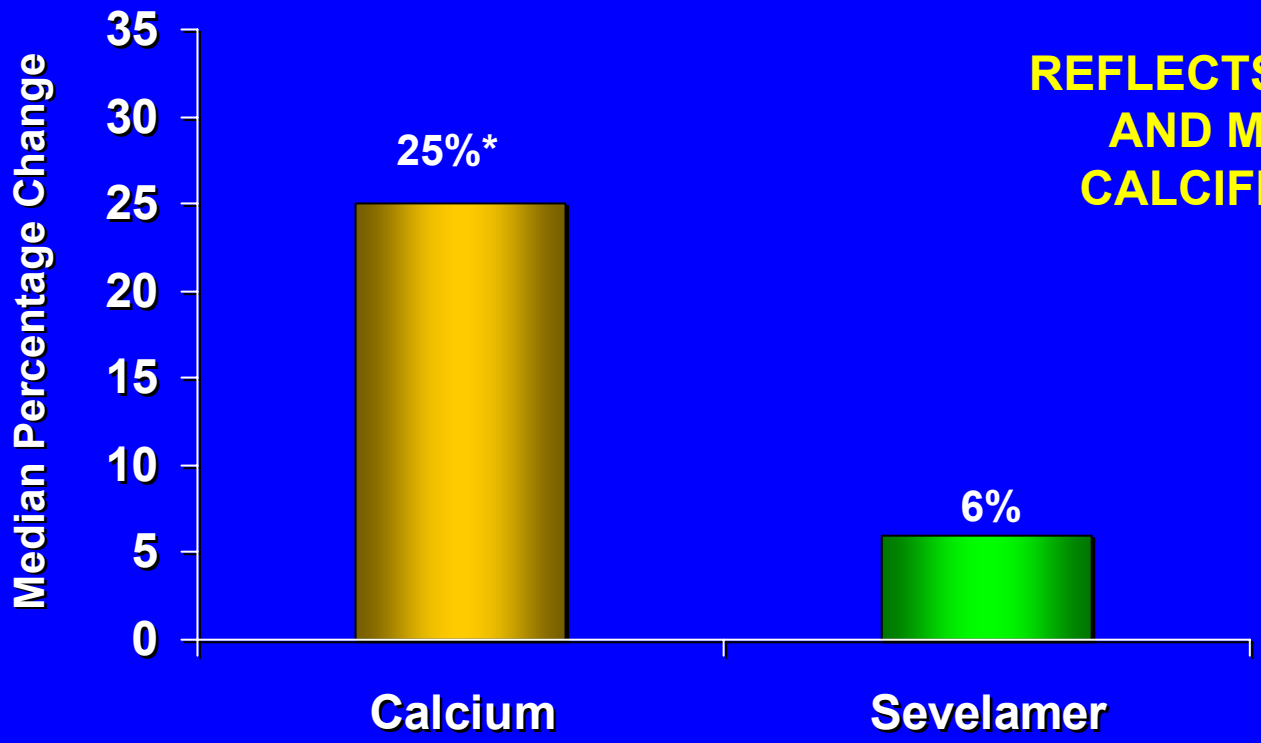


Genes Associated with Ectopic Calcification

Null Mutation	Phenotype
Matrix Gla-Protein	arterial, valve,and cartilage calcification
Fetuin	decreased serum HA inhibitory activity
Osteopontin	increased calcification of subcutaneously implanted bioprosthetic valve tissue
Osteoprotegerin	osteoporosis, vascular calcification
b-glucosidase (klotho)	vascular calcification, rapid aging
Desmin	neonatal cardiomyopathy w/calcification
Carbonic Anhydrase II	vascular calcification of small arteries

Percentage Change in Coronary Scores at 52 Weeks

In Patients with Baseline Score > 30



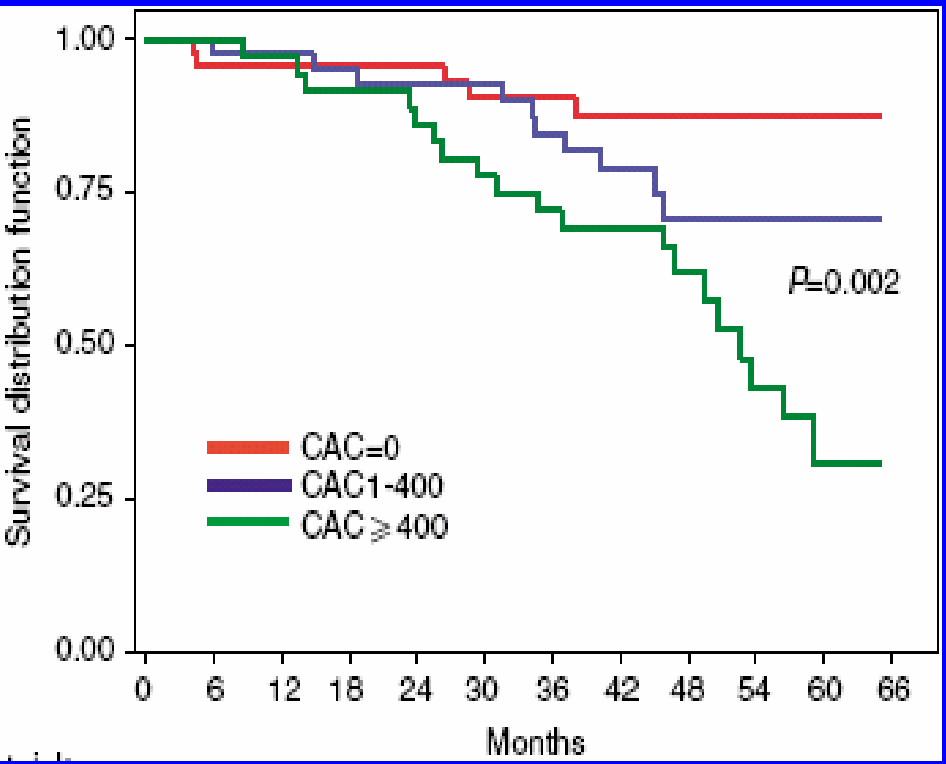
REFLECTS INTIMAL AND MEDIAL CALCIFICATION

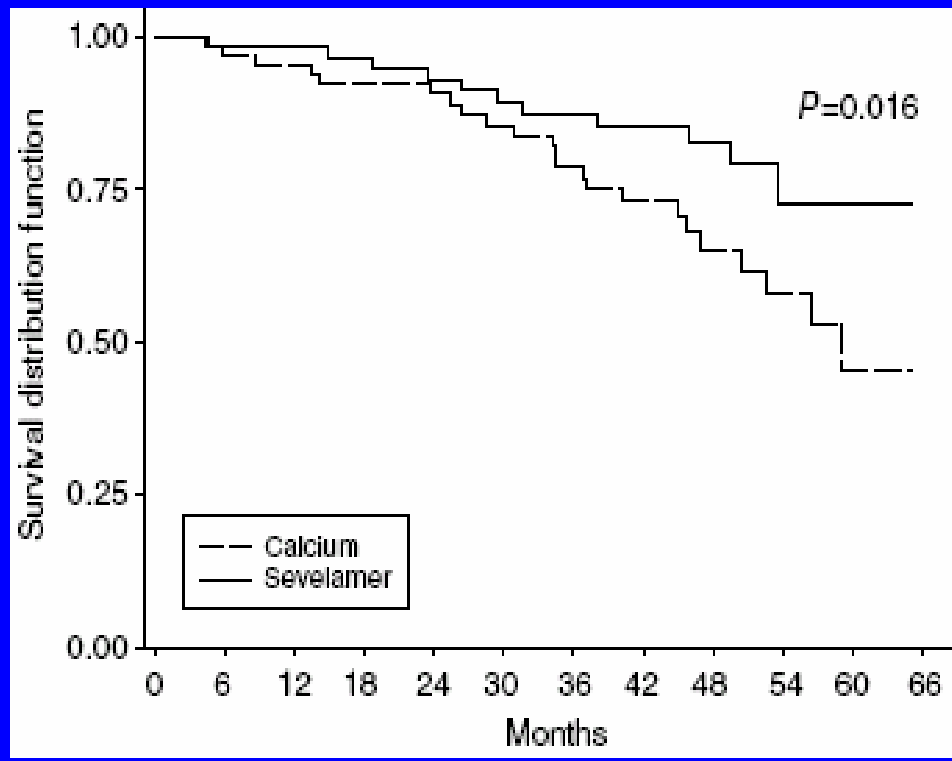
*Within treatment *P*<0.0001; between treatment groups *P*=0.02.
Patients with a baseline score >30.

Chertow GM, Raggi P, and the Treat to Goal Working Group, *Kidney Int* Vol 62; 2002

Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients

GA Block[1], P Raggi[2], A Bellasi[3], L Kooienga[4] and DM Spiegel[4]





Kidney International advance online publication, 3 January 2007;

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2004;351:1296-305.

ORIGINAL ARTICLE

Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization

Alan S. Go, M.D., Glenn M. Chertow, M.D., M.P.H., Dongjie Fan, M.S.P.H., Charles E. McCulloch, Ph.D., and Chi-yuan Hsu, M.D.

1,120,295 pts

The biggest threat to patients with CKD is not progression to ESRD

Its death from Cardiovascular disease

1,120,295 pts
Median follow up 2.84 years
(IQR 1.65 - 4.01)
3,132,192 person years

DIALYSIS	TRANSPLANT	DEATHS
3171	329	51,424
0.28%	0.03%	4.5%

N Engl J Med 2004;351:1296-305.

IN PATIENTS WITH CKD

- WE MAKE A MAJOR EFFORT TO MINIMIZE PROGRESSION TO ESRD

- WE SHOULD EXPEND AT LEAST A SIMILAR AMOUNT OF ENERGY MINIMIZING THE DEVELOPMENT OF CARDIOVASCULAR DISEASE

WHAT SHOULD WE DO ?

- **BEGIN EARLY (? GFR = 60mls/min)**
- **CONTROL OF Ca / PO_4 / PTH AXIS**
- **GLOBAL CARDIOVASCULAR PROPHYLAXIS**

Hyperlipidemia Blood Pressure Smoking
Obesity ASA Exercise Alcohol

QUESTIONS TO BE ANSWERED

- AT WHAT GFR SHOULD PO_4 CONTROL BEGIN ?
- CAN EARLY PO_4 CONTROL BE SAFELY ACHIEVED WITH Ca CONTAINING BINDERS ?
- WHAT LEVEL OF CALCIUM PHOSPHORUS AND PTH SHOULD WE TARGET ?
- WHERE SHOULD PTH BE IN THE LIST OF PRIORITIES?
- WHAT IS THE ROLE OF VITAMIN D ?
- WHAT IS THE ROLE FOR CALCIMIMETICS ?

QUESTIONS TO BE ANSWERED

IF WE CONTROL SERUM CALCIUM AND PHOSPHORUS EARLY AND TARGET THE NORMAL RANGE:

- WILL PTH REMAIN NORMAL?
- IF PTH RISES, IS THIS THE STAGE TO INTRODUCE VITAMIN D?
- WHAT OUTCOME(S) SHOULD WE FOLLOW?
- HOW TO MANAGE THE PATIENT WITH NO PREDIALYSIS CARE?

SUMMARY

- BEGIN INTERVENTIONS EARLY GFR=60mls/min
- FOCUS ON Ca AS WELL AS PO_4
- PTH MAY BE LESS IMPORTANT OUTCOME
- AGRESSIVELY ADDRESS GLOBAL CARDIOVASCULAR RISK lipids, obesity, smoking, alcohol, exercise, aspirin
- ADDITIONAL STUDIES NEEDED TO CLARIFY ROLE OF:
  - VITAMIN D
  - CALCIMIMETICS
  - PRIORITY OF PTH