Kidney Bone Disease
What happens when the kidney fails?

- Progression of kidney damage >> mineral metabolism
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  - Lanthanum and the calcium loading concept

M.E. De Broe
Stockholm
31 March 2009

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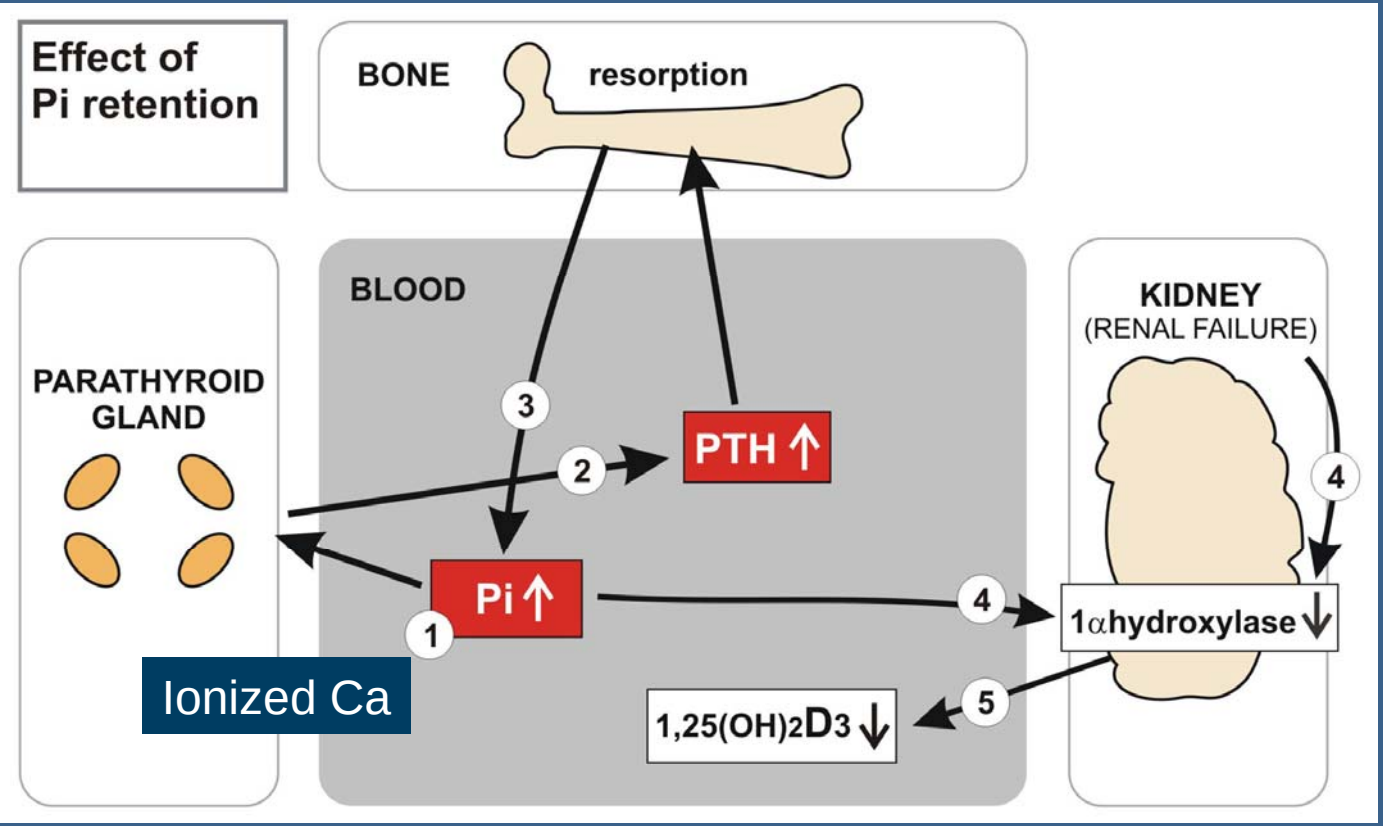
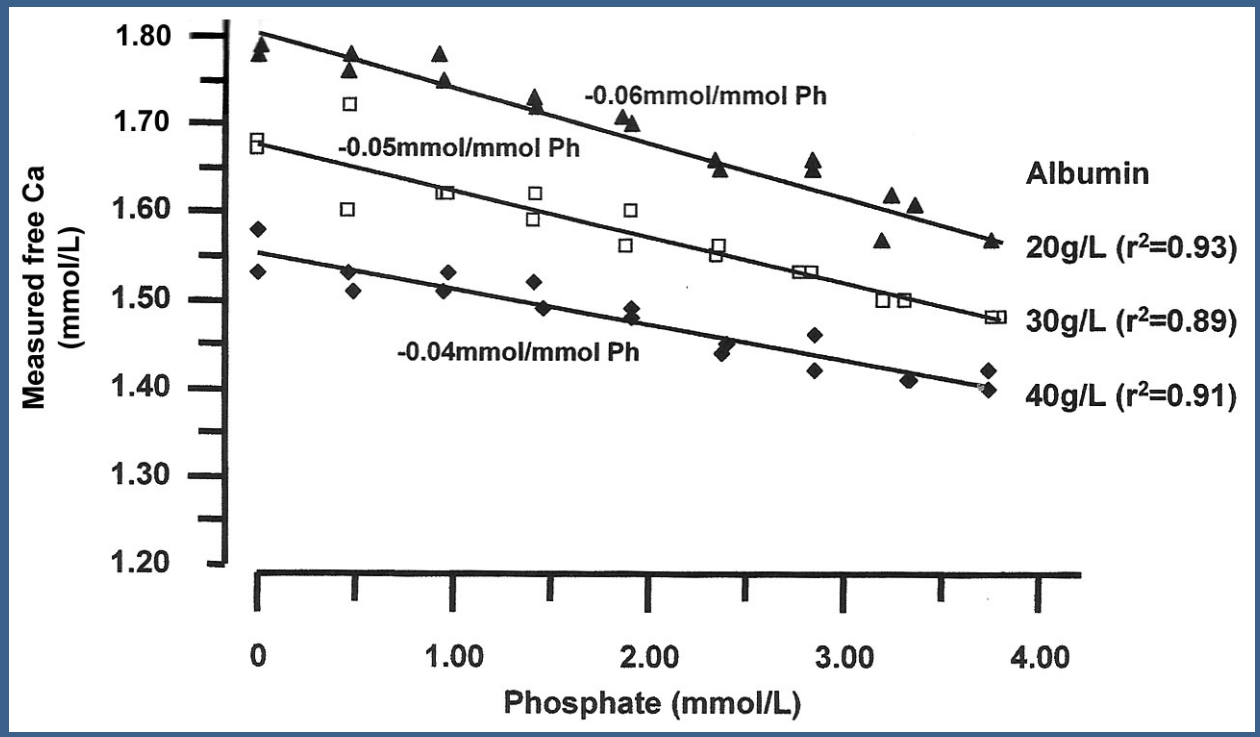
Consequences of phosphate accumulation in chronic renal failure



High phosphate levels due to the phosphate accumulation in renal failure (1) increase the PTH secretion by the parathyroid glands (2). The resulting increase in osteoclast activity will raise the phosphate levels further (3). Renal failure itself, together with increased serum phosphate levels, leads to a decrease in 1-✂ hydroxylase activity (4), resulting in reduced 1,25-(OH)2 vitamin D3 levels (5)

DDW2078

In vitro effect of increasing phosphate concentration on free calcium



pH 7.4

Fixed total calcium 2.6 mmol/L

Stronger effect of phosphate at low compared to normal albumin concentrations

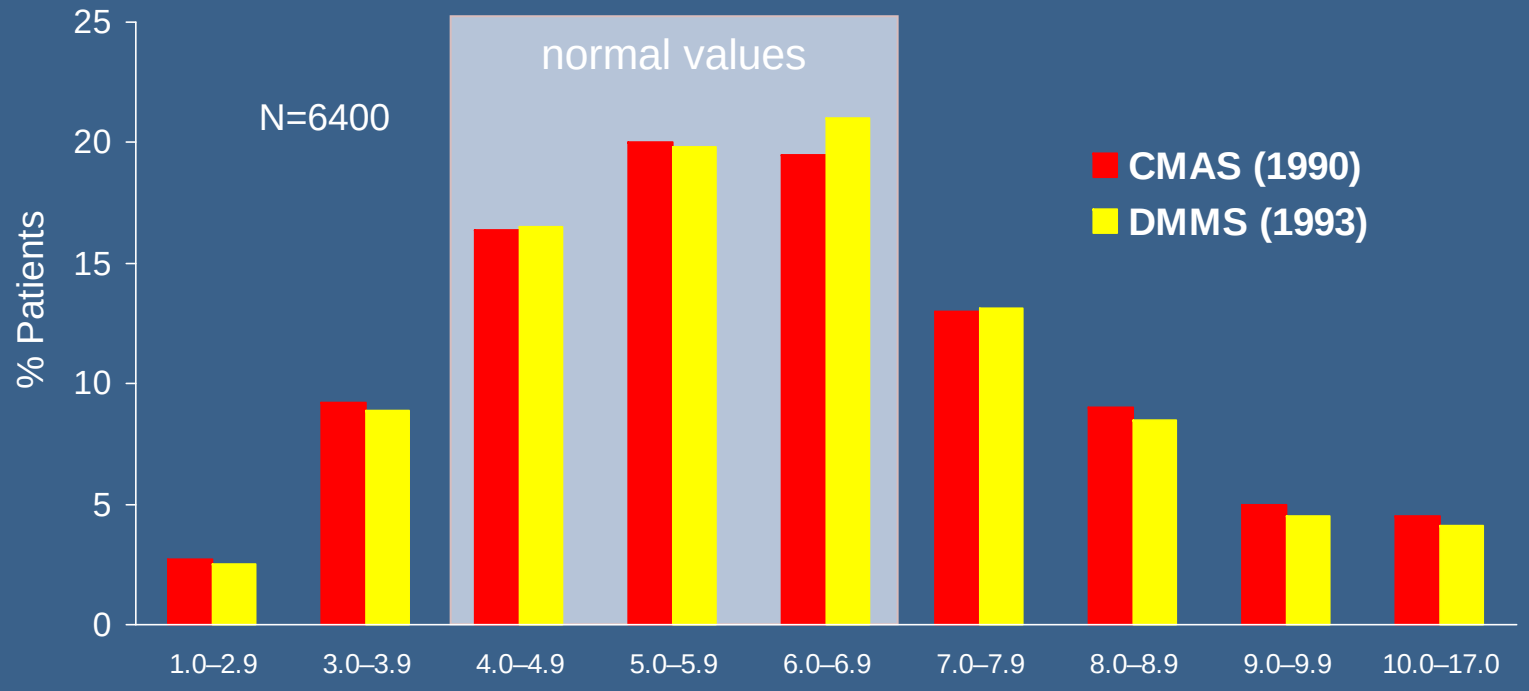
Normal Ps=1.8 mmol/l

Ferrari P et al, Kidney Int 2007

DDW3569

Distribution of Serum Phosphorus

From the U.S. Renal Data System:
Case Mix Adequacy Study (CMAS) and
Dialysis Morbidity and Mortality Study (DMMS)

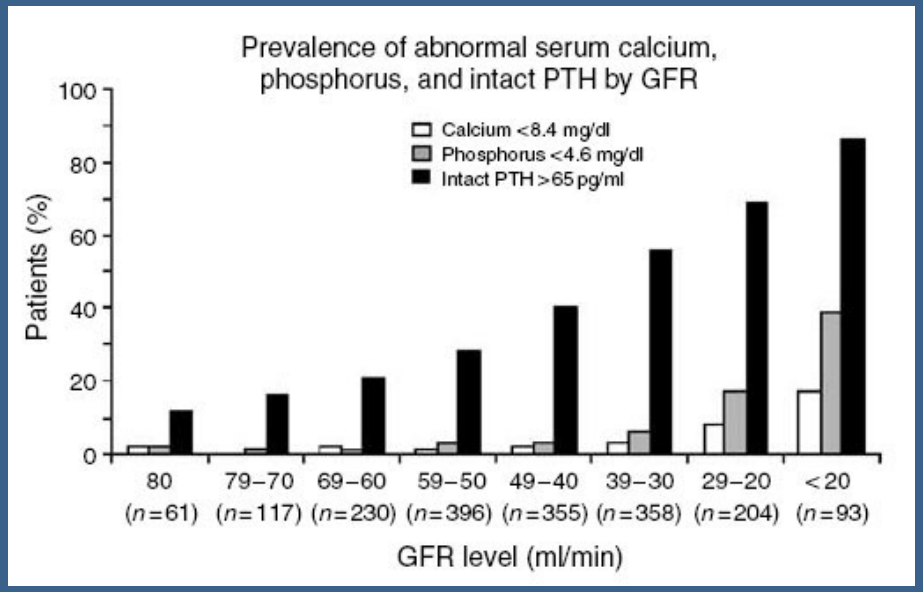


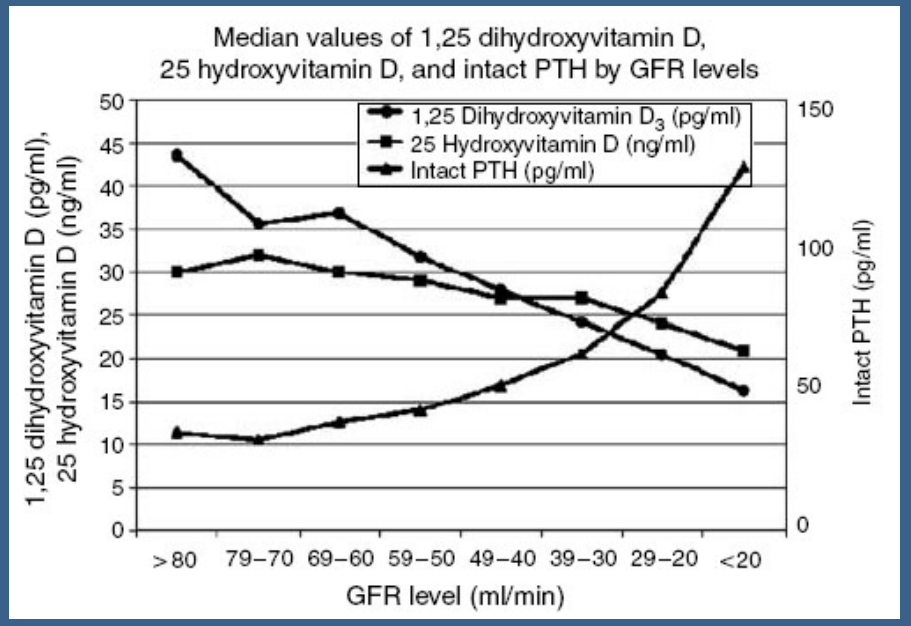
Lower than 1.80 mmol/L

Hyperphosphatemia ≈ ↑ morbidity

Block GA et al. Am J Kidney Dis. 1998;31:607-617.

Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: *Results of the study to evaluate early kidney disease*





Levin A et al, Kidney Int 71: 31-38, 2007

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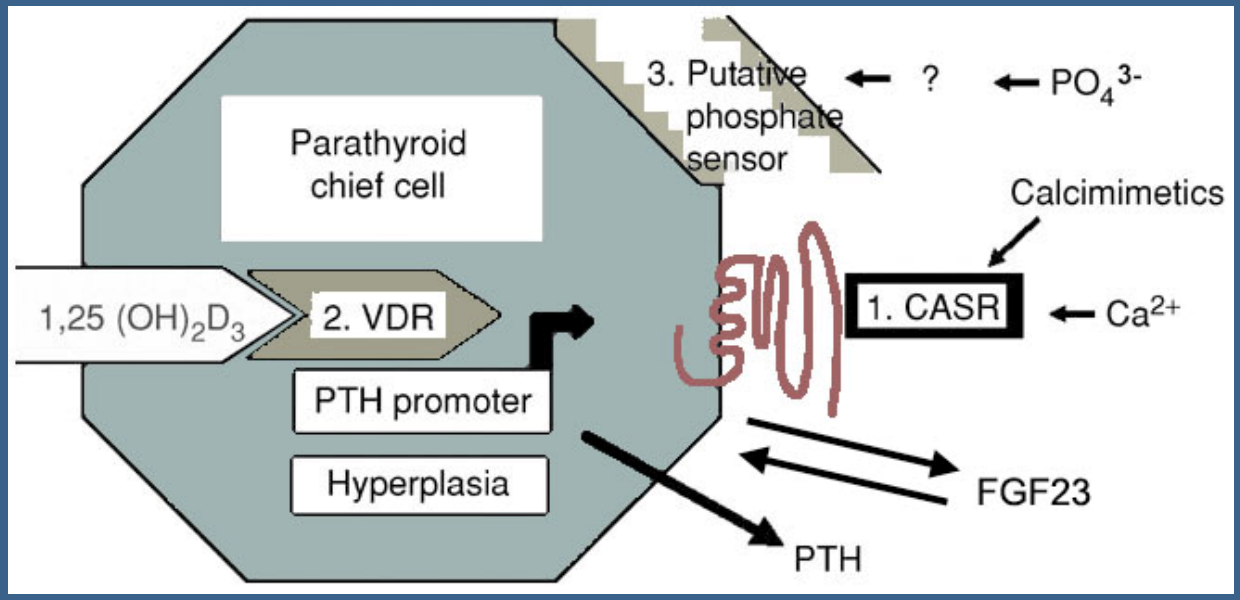
DDW3569

PTH secretion, PTH gene expression, parathyroid gland hyperplasia



1. CASR cell suface G protein –coupled receptor extrac. Ca++
2. Vitamin D receptor nuclear receptor controlling gene transcription
3. Uncharacterized phosphate sensor
4. FGF23 is a negative regulator of parathyroid function

Quarles LD: Kidney Int 68 (S96): S24-S28, 2005

Importance of ionized calcium dependent signaling

Vitamin D dependent pathways play a 2ary role

	VDR –/– (Vit D deficiency)	1αOHase –/–
Calcemia	↓	↓
Phosphatemia	↓↓	↓↓
PTH	↑↑	↑↑
Osteomalacia	+	+
Gland hyperplasia	+	+
Calcitriol	↑↑	↓↓undetectable

Feeding 2% calcium normalizes everything; signaling through CaSR is sufficient to prevent SHPT and gland hyperplasia in tissues incapable to respond to Vit D

Calcitriol normalizes everything; Ca administration almost everything

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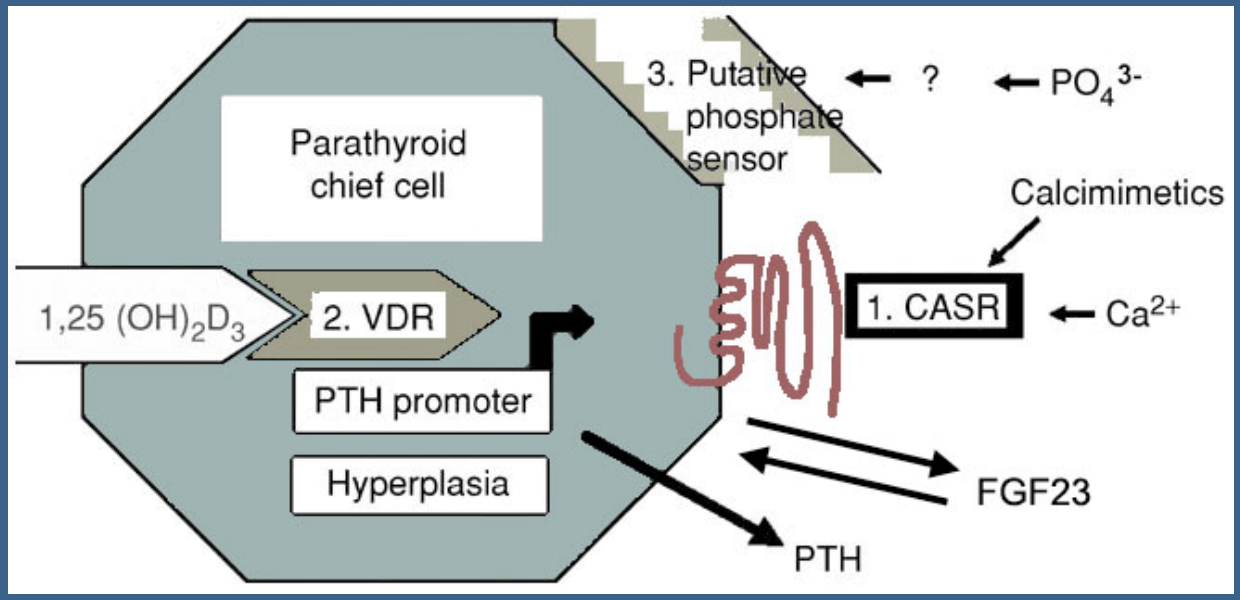
PTH secretion, PTH gene expression, parathyroid gland hyperplasia



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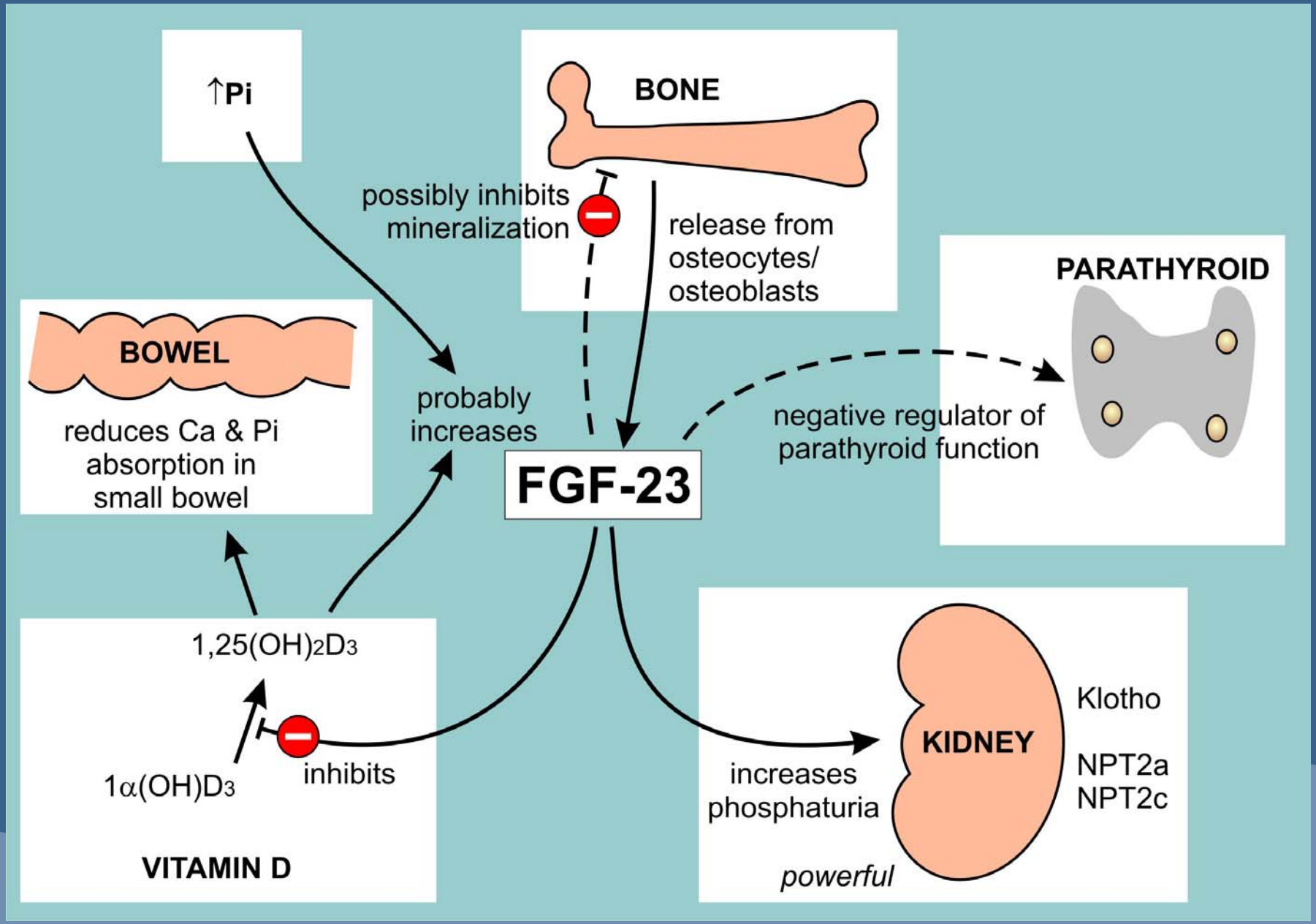
Quarles LD: Kidney Int 68 (S96): S24-S28, 2005

Fibroblast growth factor 23



FGF 23

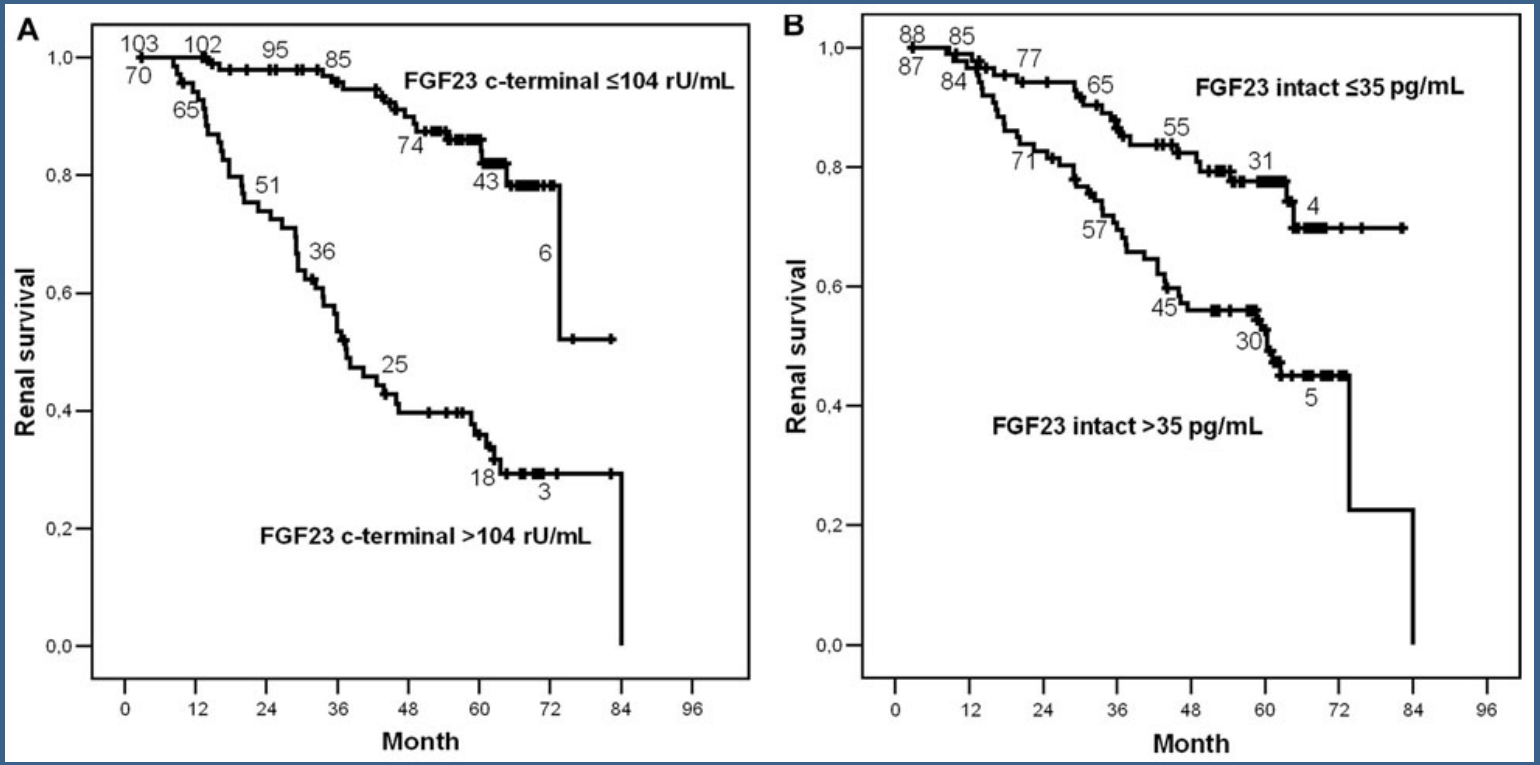
- -FGF 23 early incr.--- normalization Ps

- Vitamin D Levels decrease--- FGF 23 excess ---
  -renal mass?

- Posttransplant –hypoP – PTH incr.
- 1,25 VitD decrease
- high FGF23

- FGF23 early incr in CKD –marker of disorder
- of P metabolism

FGF-23 predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease study



Kaplan-Meier curves of renal end points in patients with below and above optimal cutoff of plasma c-terminal (A) FGF23 concentrations and for intact (B) FGF23 concentrations below and above the median

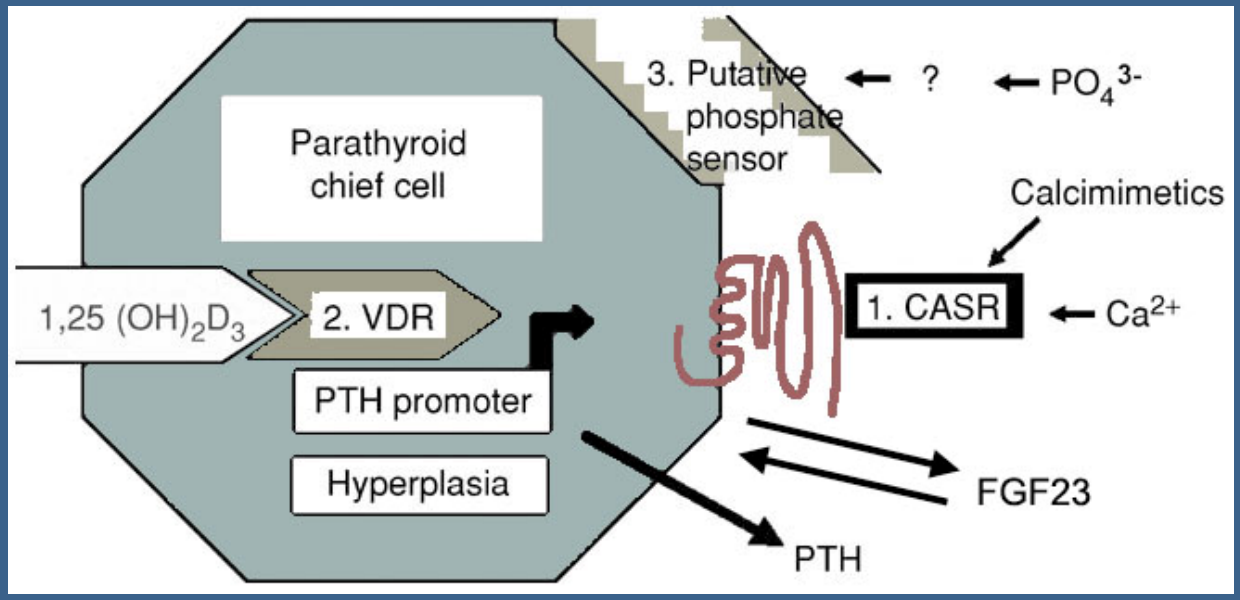
Fliser D et al: JASN 18: 2600-2608, 2007

FGF 23 and Clinical Nephrology

- Dose dependent increase risk of death in HD patients
- FGF 23 may be a superior marker for disorders of P metabolism related CVD in CKD
- FGF23 as biomarker of CKD progression
- Phosphate binding decrease FGF 23 levels

NEJM 359 ,584 ,2008
JASN 18 , 2600 , 2007
Kidn Intern 69 , 531 , 2006
Atheros. 2009

PTH secretion, PTH gene expression, parathyroid gland hyperplasia



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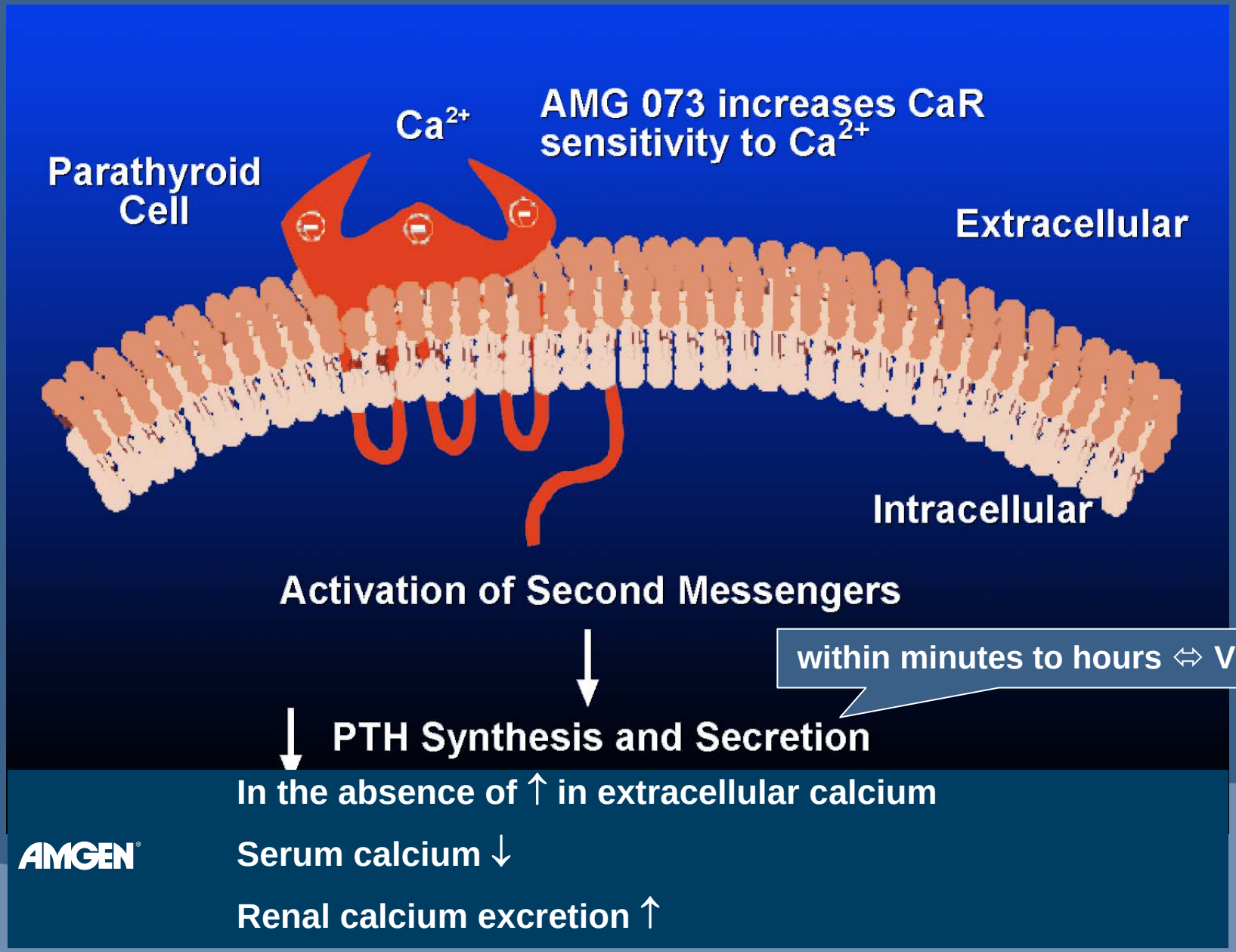
Quarles LD: Kidney Int 68 (S96): S24-S28, 2005

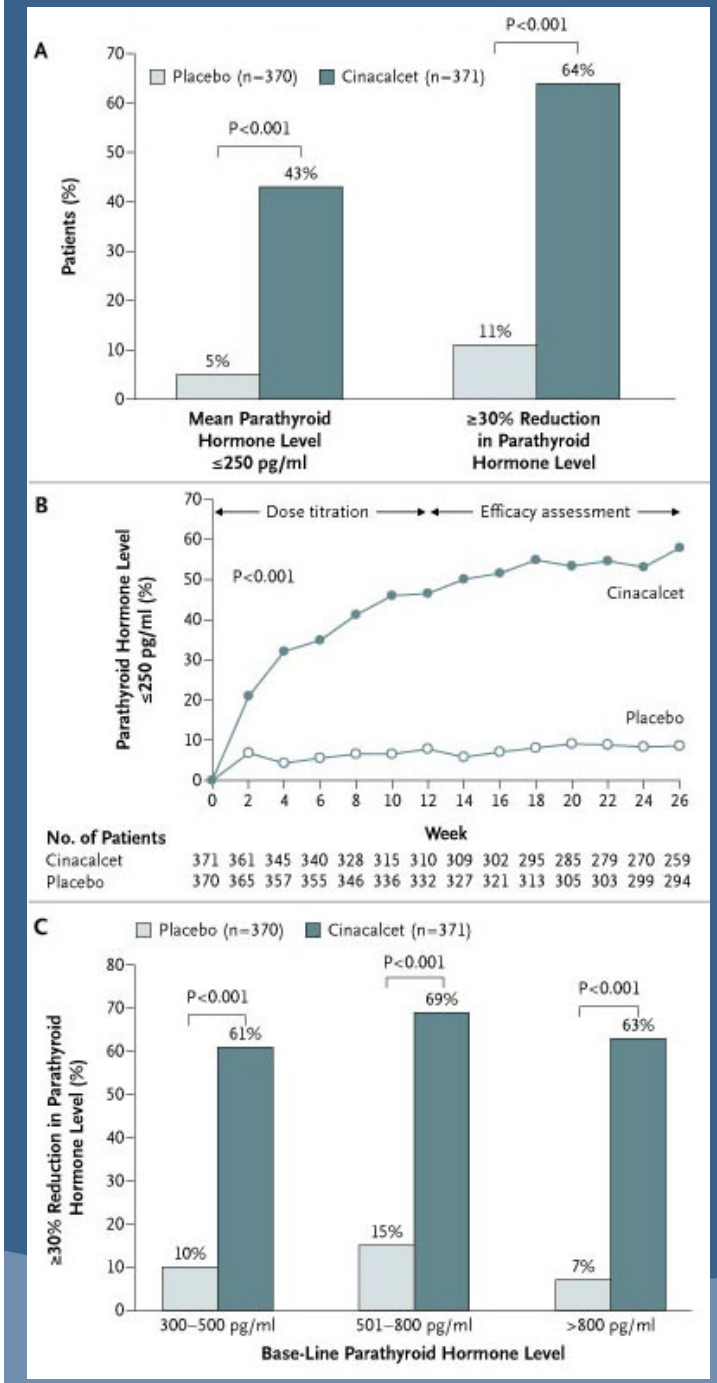
Calcimimetic agents and secondary hyperpathyroidism

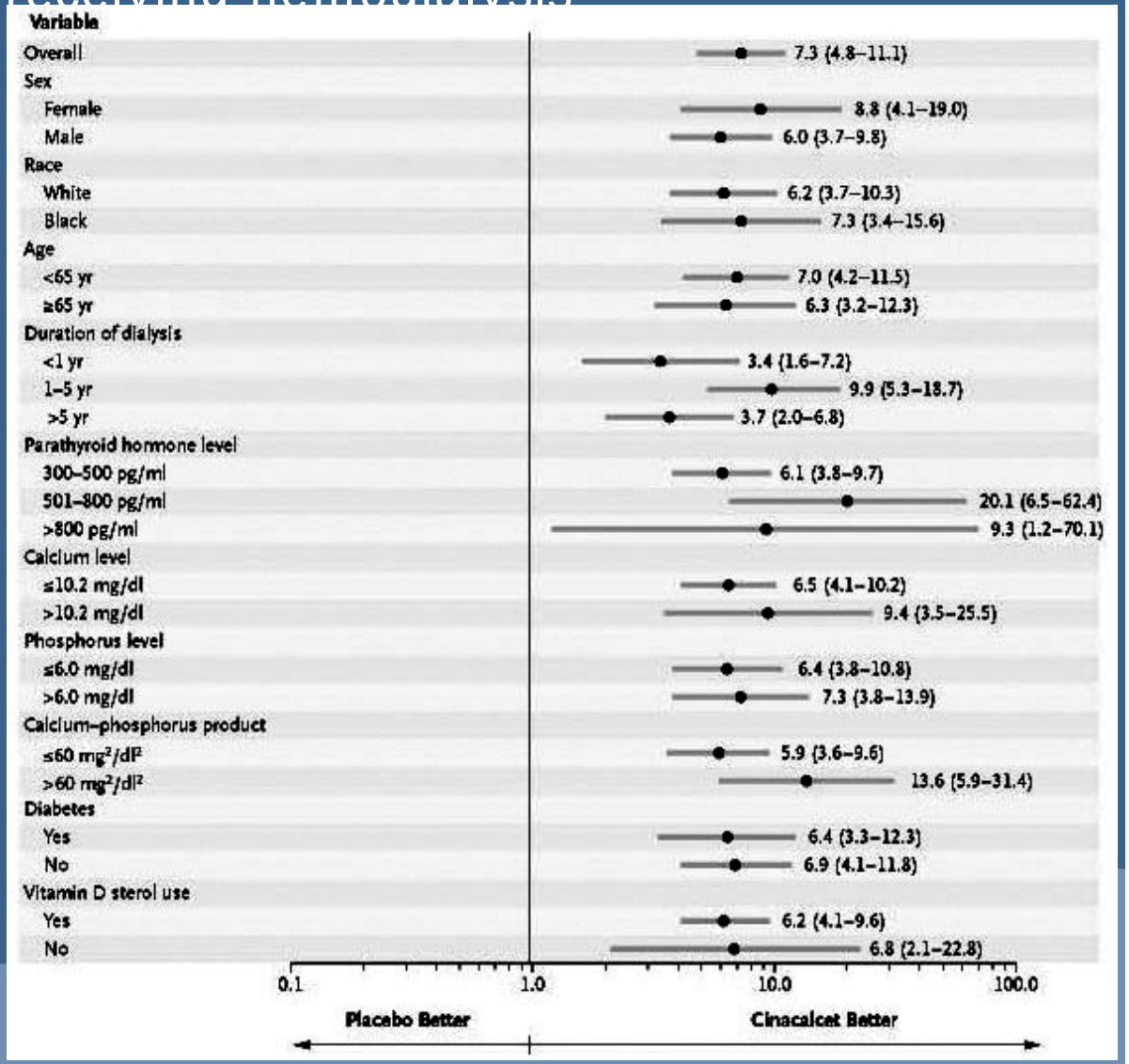


AMGEN®

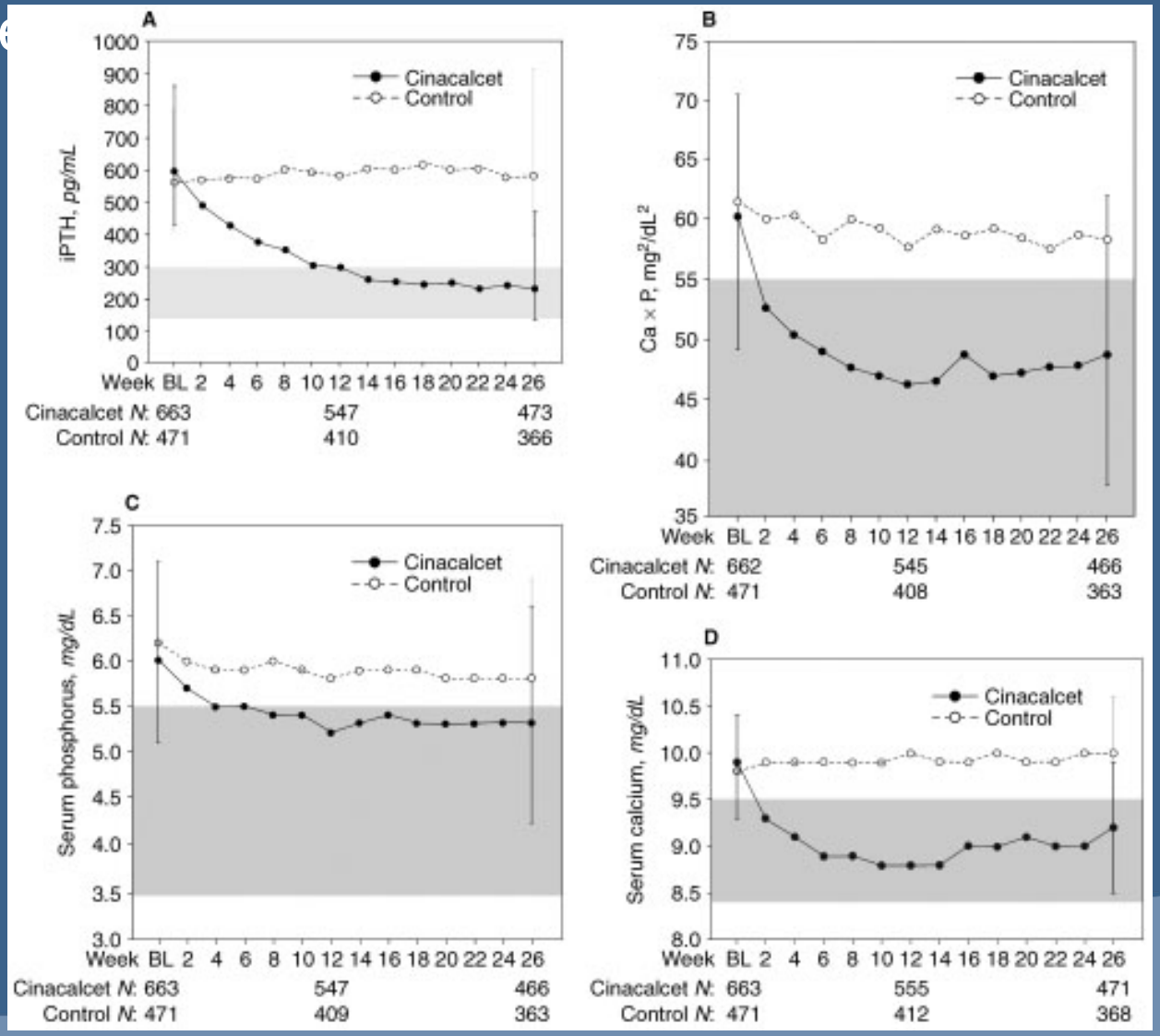
Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis

Block GA et al. New Engl J Med 350: 1516-1525, 2004





Achieving NKF/DOQI™ bone metabolism and disease



Moe SM et al: Kidney Int 67: 760-771, 2005

Long-term treatment of secondary hyperparathyroidism with the calcimimetic cinacalcet HCl

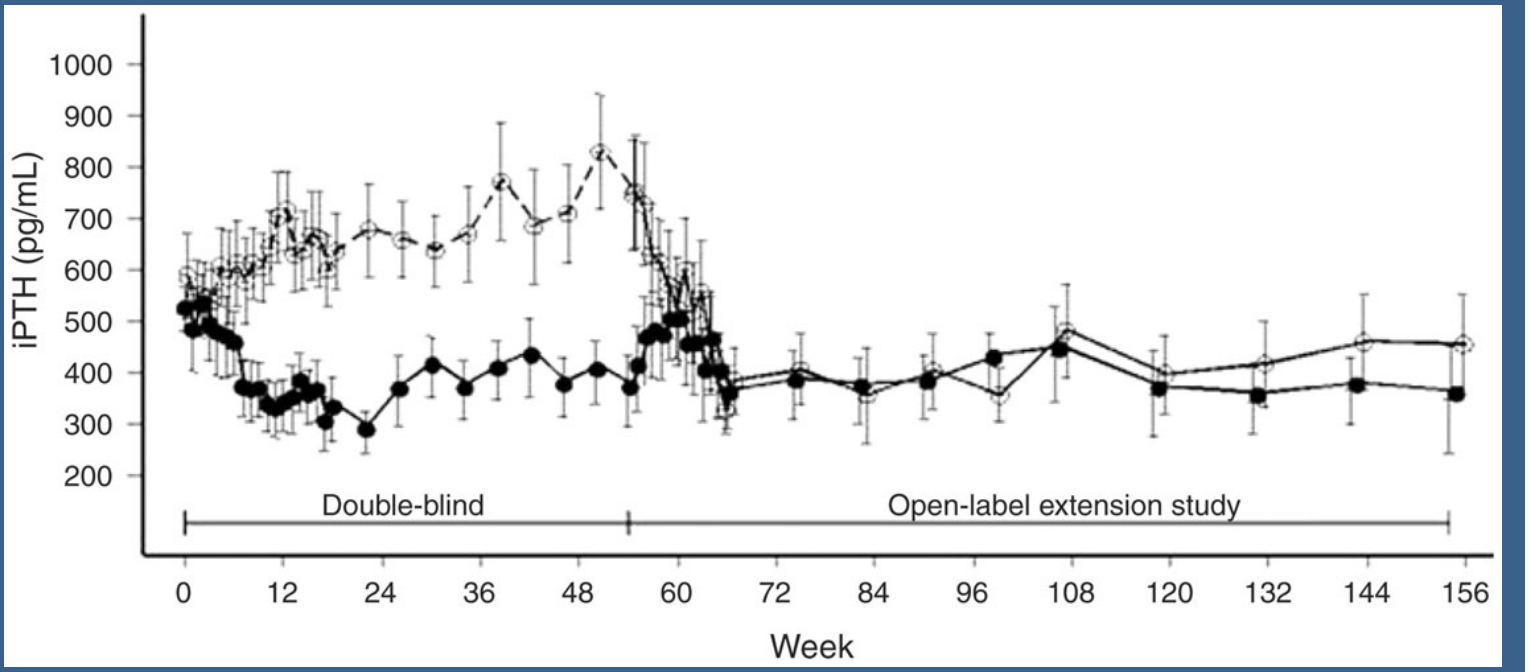


Table 3. The proportion of patients who achieved the NKF-K/DOQI™ targets

Recommended NKF-K/DOQI™ targets	Baseline of qualifying study *n* (%)	Week 52 *n* (%)	Week 100 *n* (%)
PTH ≤300 pg/ml	6 (10%)	30 (52%)[a]	35 (59%)[a]
Serum calcium ≥8.4 to ≤9.5 mg/dl	25 (42%)	23 (40%)	22 (37%)
Serum phosphorus ≥3.5 to ≤5.5 mg/dl	19 (32%)	21 (37%)	22 (37%)
Ca×P <55 mg^2/dl^2	25 (42%)	32 (56%)	31 (53%)

Moe SM et al: Nephrol Dial Transplant 20, 2186-2193, 2005

Calcimimetics – Secondary hyperparathyroidism

- Bioavailability is low
- Metabolism is variable – pharmacokinetics?
- Long term use
- Hypocalcemia – calcium load ? uptake in bone?
  5%: < 7.5 mg%
- Phosphate handling – dialysis – stage 3 - 4 CKD
- hyperphosphatemia, hypocalcemia, hypercalciuria
- Effects on bone – vascular calcification
- Effects on other systems – calciuria
- up and down ←→ persistent effect of PTH

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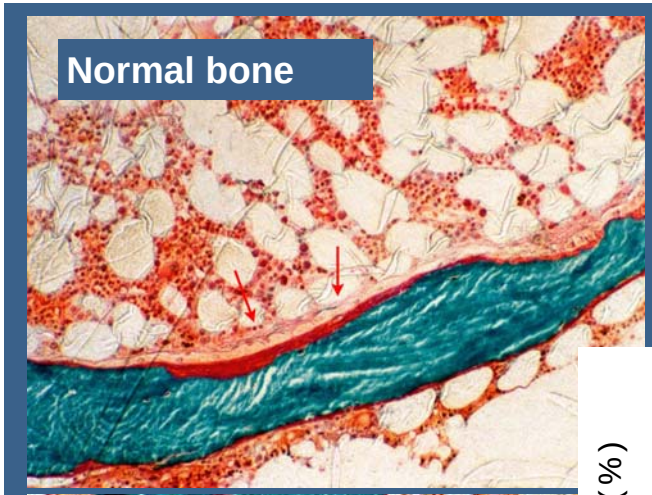
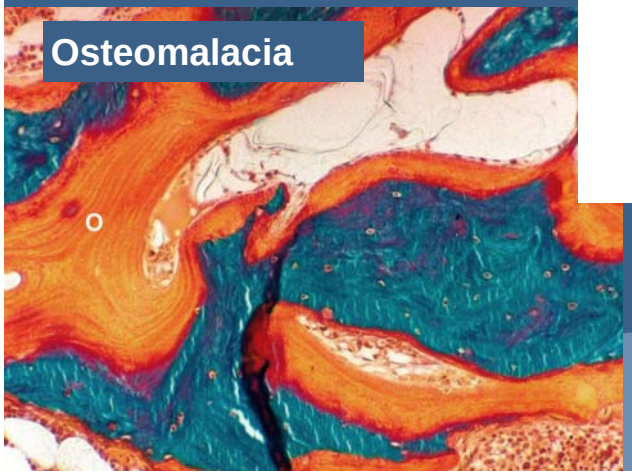
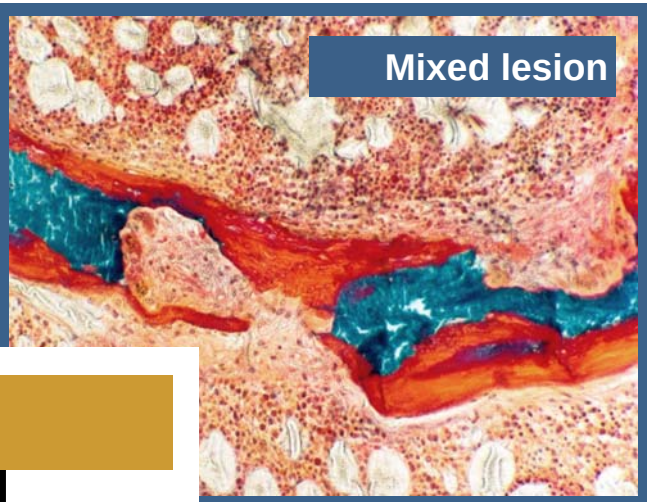
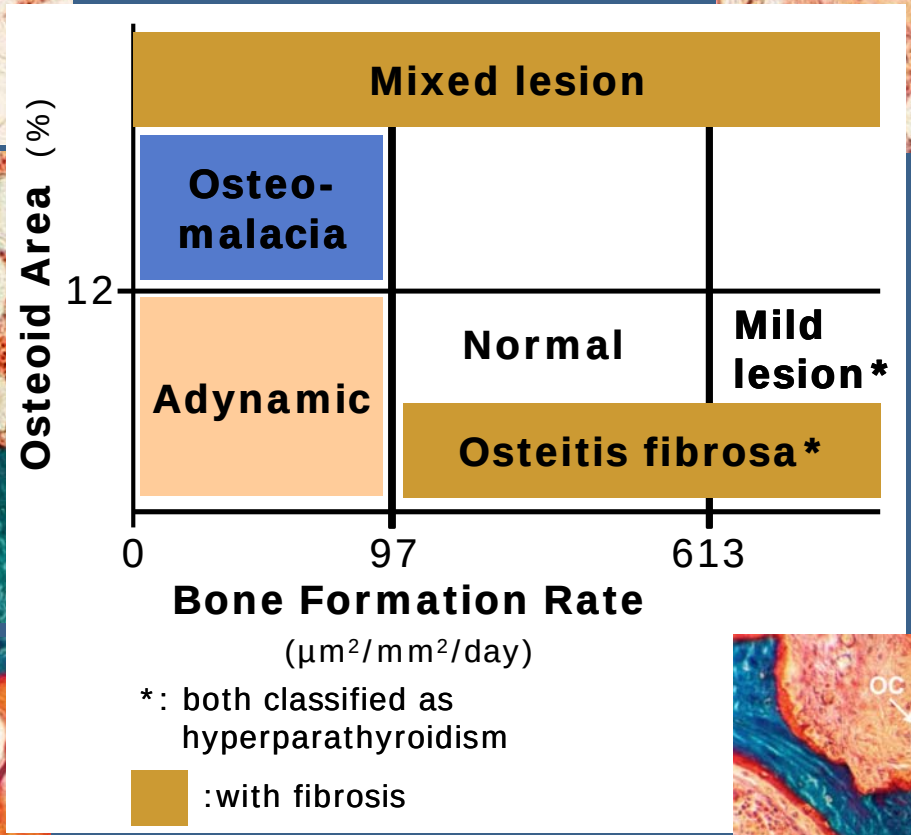
Classification of renal osteodystrophy









Summary of published prevalences (%) of different types of ROD over the years in *dialysis patients*

Reference (et al)	Type of patients	N	Index of Al presence	Prevalence			
				ABD	Normal	Osteomal.	OF/Mixed
Sherrard, 1972	HD	67		0%		24%	67%/9%
Liach, 1986	HD	142	Major. of OM & ABD	7%		25%	68%
Salusky, 1988	CAPD (children)	44	23%	11%	16%	9	64%/0%
Moriniere, 1989	HD	42	9.5%	24%		0	76%
Maluche, 1992	HD+CAPD	1803 1984y 1991y	 56.4% 62.2%	 5% 20%		 15% 2%	 27%/53% 22%/56%
Sherrard, 1993	HD CAPD	117 142	15% 25%	36% 60%		3% 6%	50%/11% 30%/4%
Torres, 1995	HD CAPD	49 32		32% 48%		12% 10%	44%/12% 32%/10%
Couttenye, 1996	HD	103	5%	37%	13%	10%	20%20%
Coen, 1998	HD	41	0%	11%		11%	56%/22%
Canavese,1998	HD	80	35%	9%		18%	36%/37%
Sanchez, 2000	CAPD	57	14%	63%		0%	37%
Gerakis, 2000	HD	62	34%	23%		3%	64%/10%
Changsirikul-chai, 2001	HD CAPD	39 17	3.5%	41%		4%	30%/25%
Ballanti, 2001	HD	37	0%	14%		19%	43%/24%

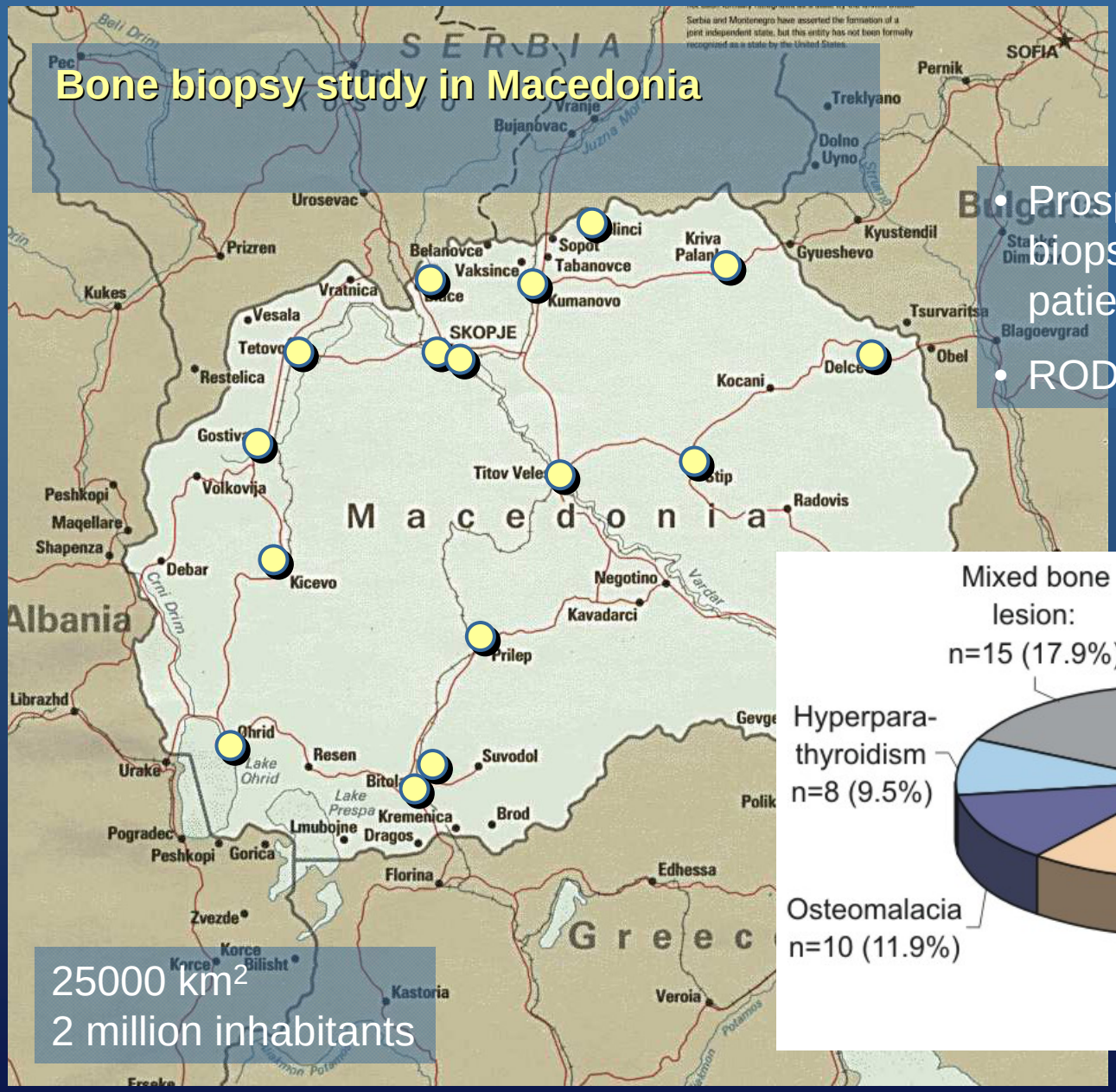
GS Spasovski, PhD thesis, University of Skopje, Macedonia, 2002

Summary of published prevalences (%) of different types of ROD over the years in *patients with chronic renal failure not yet in dialysis*

Reference (et al)	Type of patients	N	Index of Al presence	Prevalence			
				ABD	Normal bone	Osteomal.	OF/Mixed
Eastwood, 1982	CRF	38		5%	8%	44%	43%
Mora Palma, 1983	ESRD	327		0%	12%	34%	54%
Dahl, 1988	ESRD	60	0%		18%	12%	70%
Hutchison, 1991	ESRD	34	ND	16%		22%	53%/9%
Cohen-Solal, 1992	ESRD	27	0%	0%	33%	11%	37%/10%
Hutchison,1993	ESRD	30	6.6%	27%		7%	50%/13%
Hernandez, 1994	ESRD	92	4.3%	33%		11%	56%
Torres, 1995	ESRD	38	3.4%	48%		2%	40%/10%
Hamdy, 1995	CRF	176	2%	4.4%	25.0%	0.6%	55.8%/14.2%
Coen, 1996	CRF	76	0%	12%	13%	9%	69%
Shin, 1999	ESRD	58	0%	24%	9	10%	45%/12%
Ballanti, 2001	ESRD	27	0%	22%		11%	8%/59%

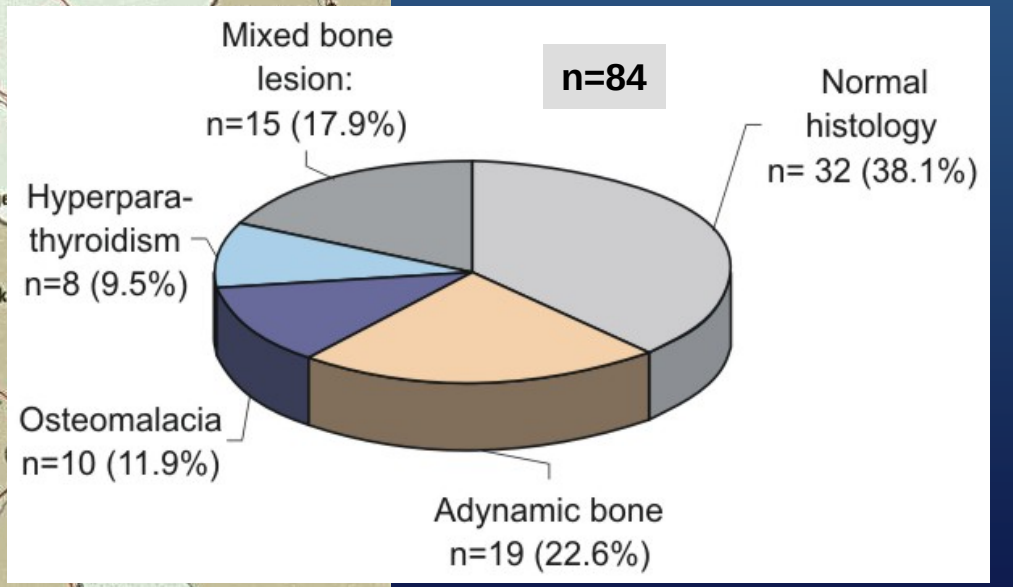
GS Spasovski, PhD thesis, University of Skopje, Macedonia, 2002

Bone biopsy study in Macedonia



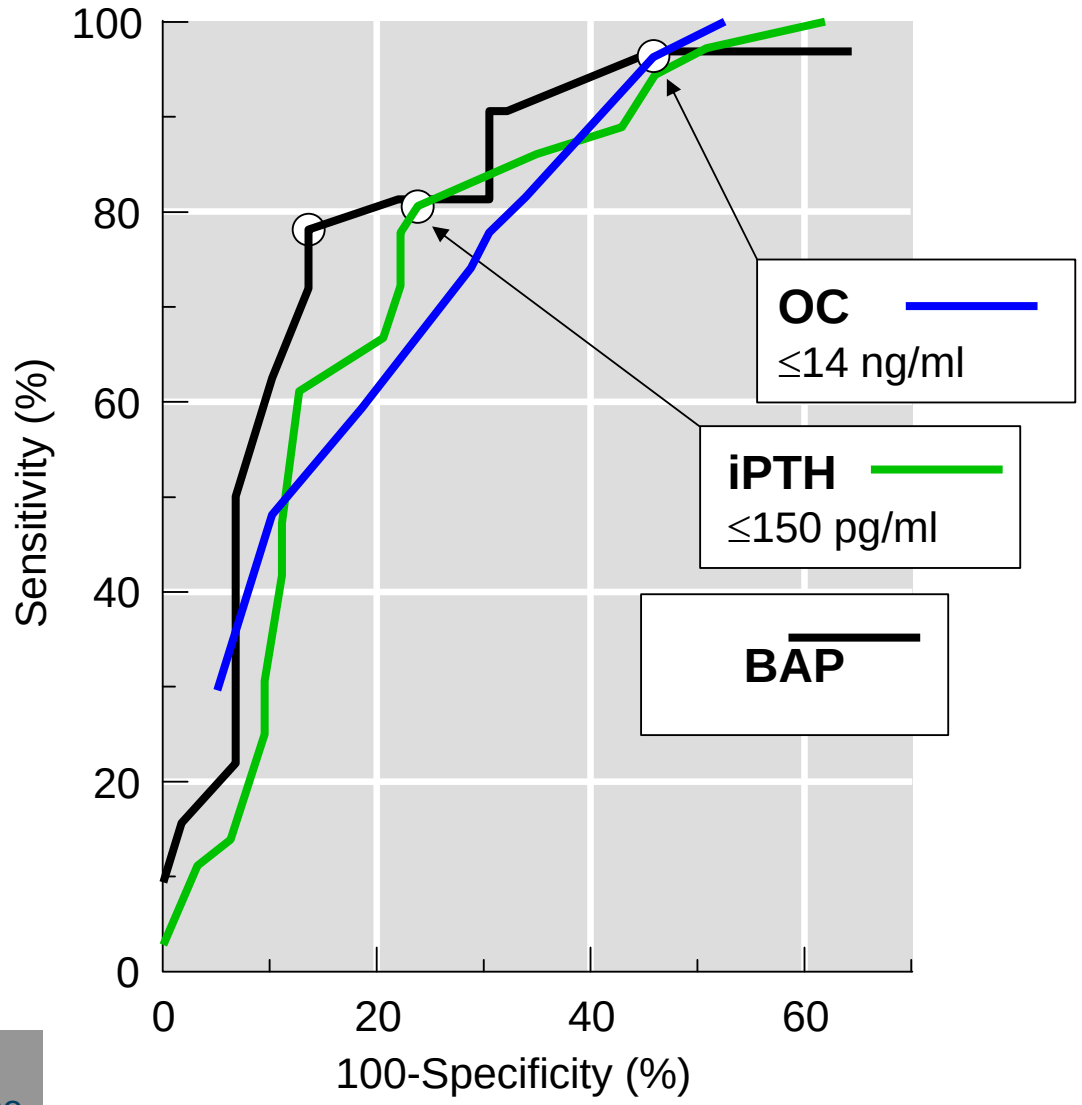
25000 km²
2 million inhabitants

- Prospective unselected bone biopsy study of all pre-dialysis patients over 9 months
- ROD histology



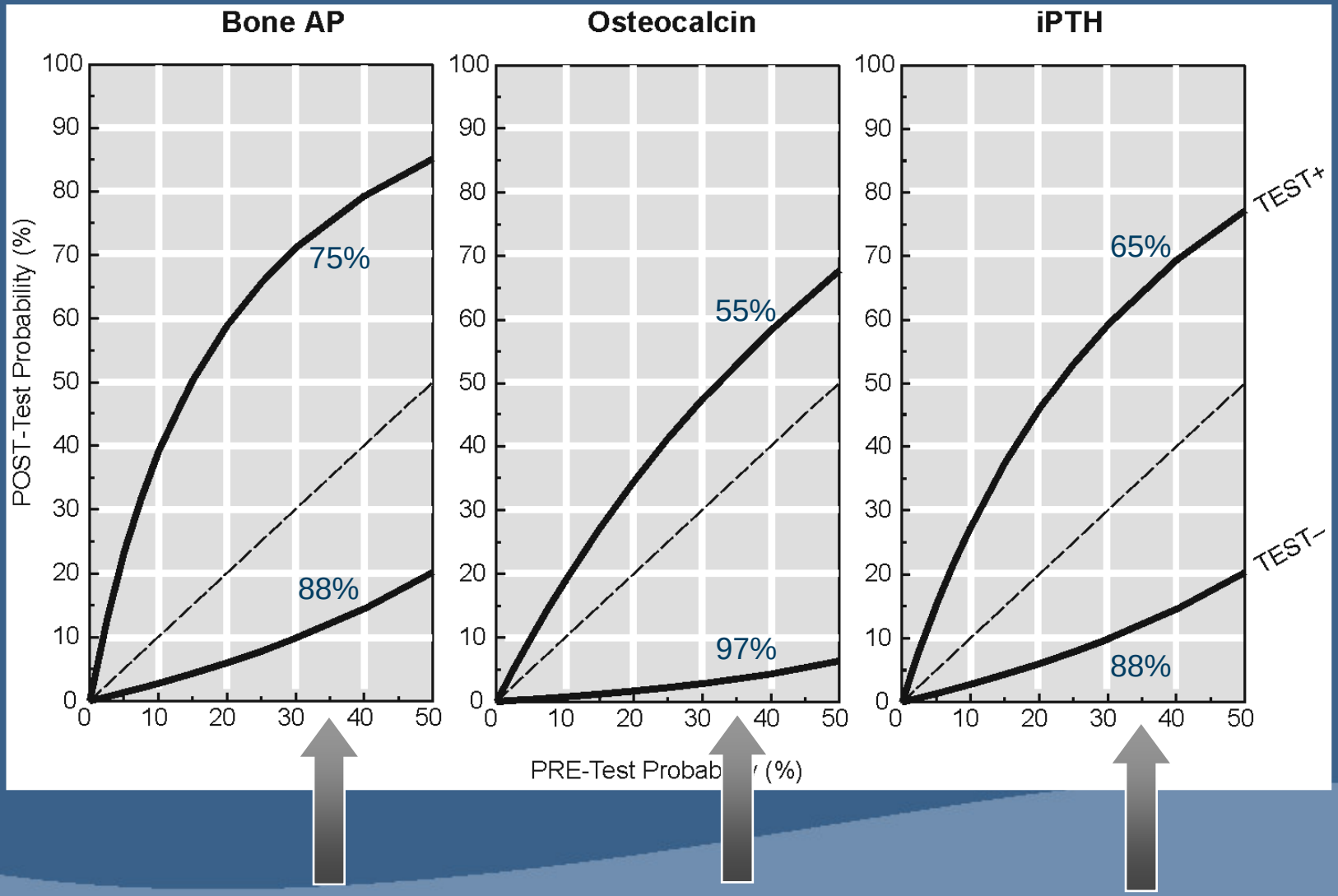
Spasovski GB et al, Neprol Dial Transplant, 2003
Bervoets A et al: Am J Kidney Dis, 2003

Diagnosis of adynamic bone disease in *hemodialysis* patients



OC: Osteocalcin
BAP: Bone alkaline phosphatase

Predictive values of biochemical markers of adynamic bone in *hemodialysis* patients



Couttenye et al, NDT 1996

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- Use of non calcium containing Phosphate binders
- Calcium load through dialysate
- peritoneal dialysis (2.5 – 3.0 mEq/l / serum iCa 1.8- 2.5 mEq/l)
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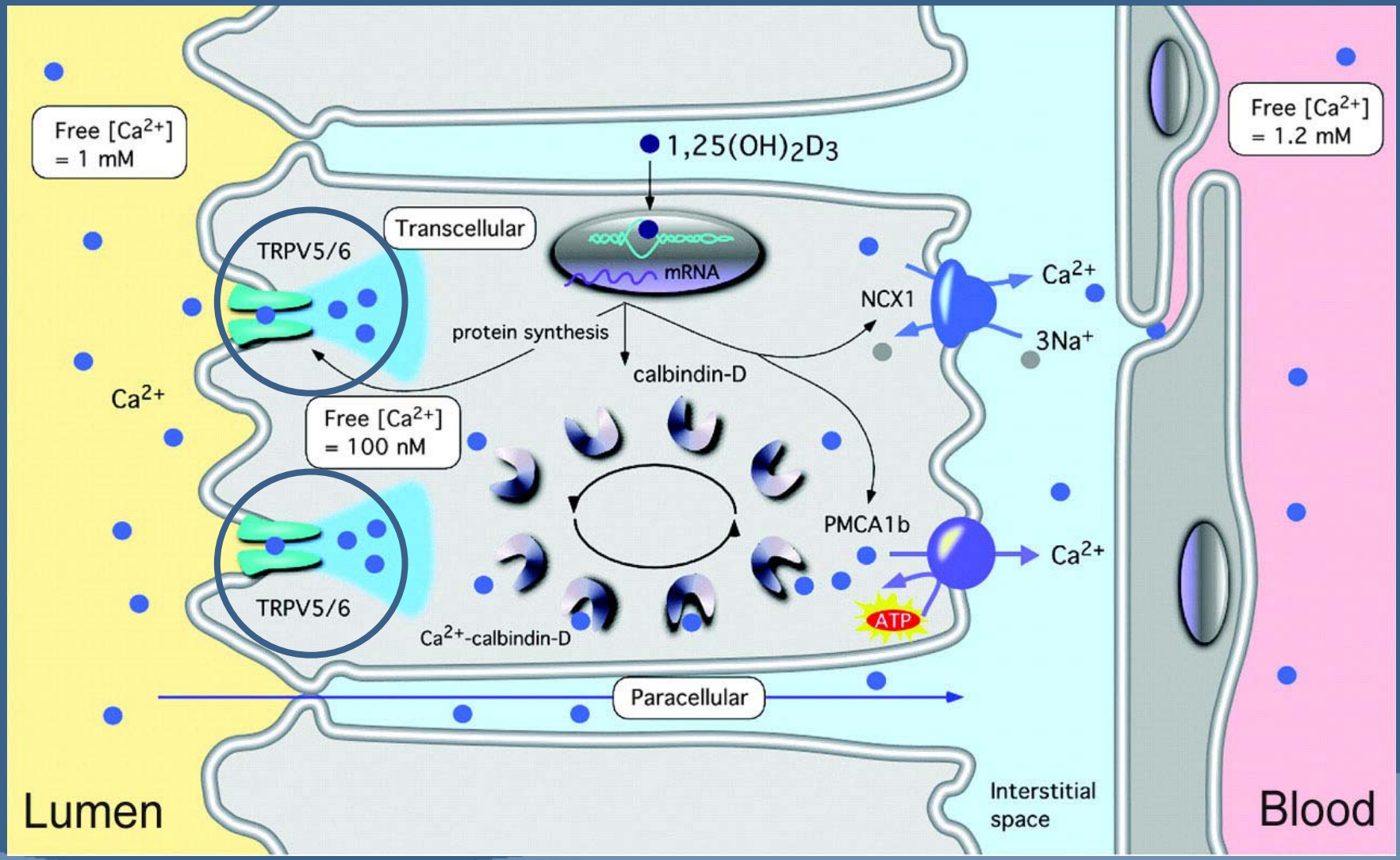
Calcium absorption across epithelia

Mechanism of epithelial Ca^{2+} transport



Hoenderop JG et al: Physiol Rev 85: 373-422, 2005

Calcium sensing receptor

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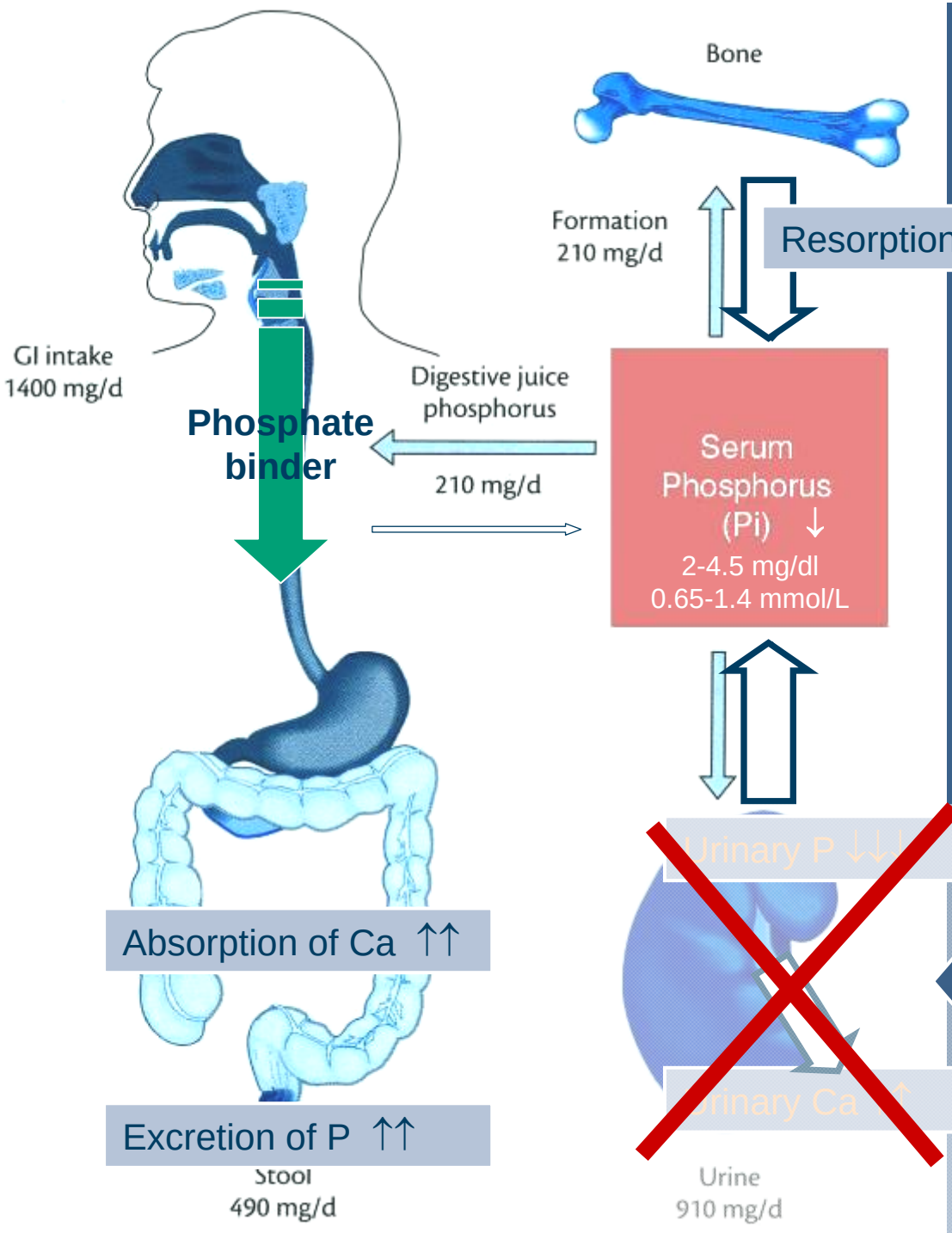


Effect of phosphate binder

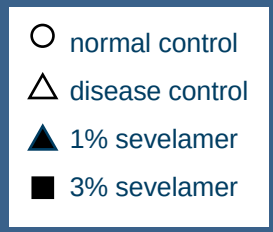
- Ø Bone Demineralization
- Ø Osteomalacia

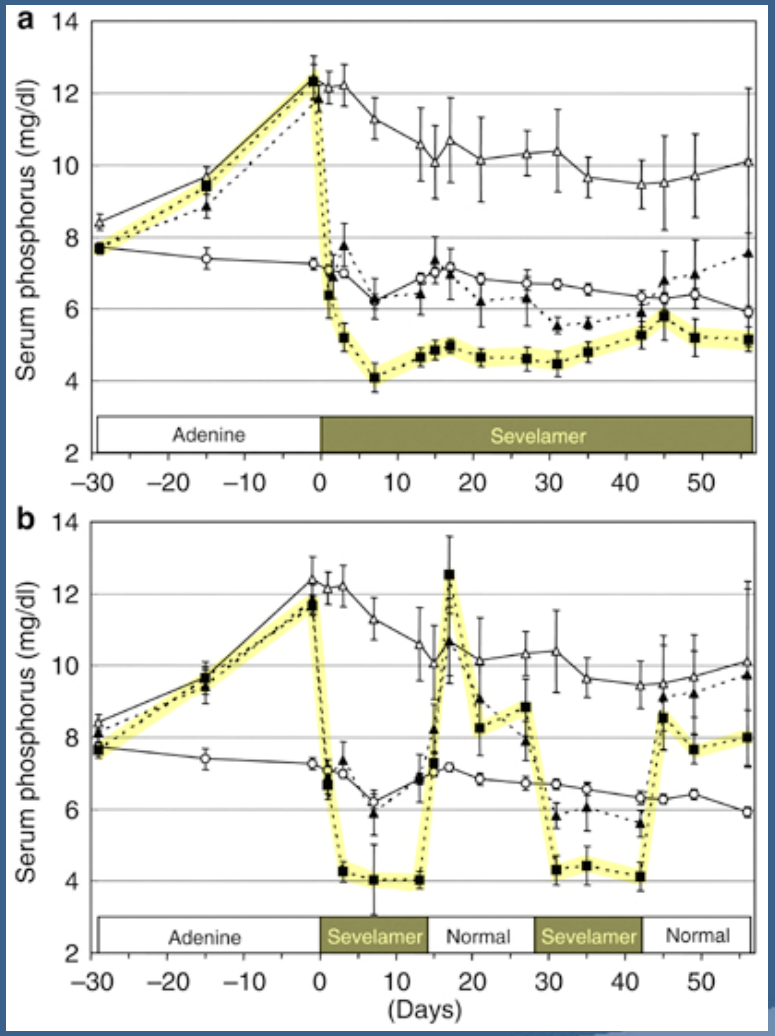
Foldes J et al: Bone 12: 67-71, 1991

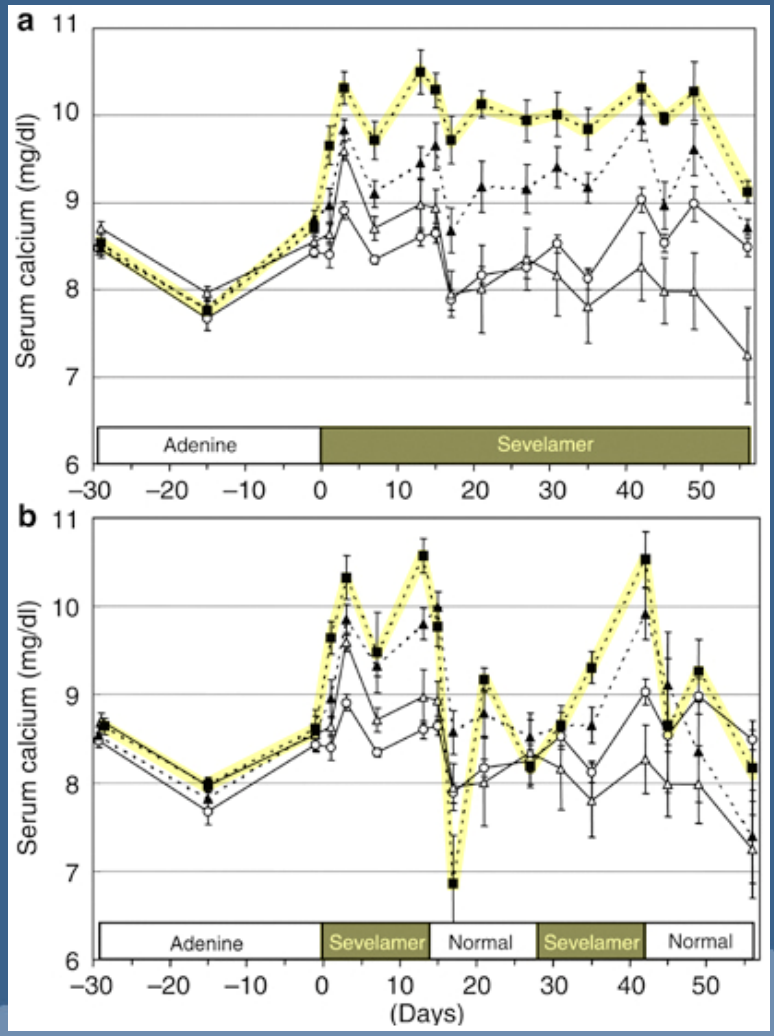
DIALYSIS PATIENT

Evidence for a phosphorus-depletion syndrome in man.
New Engl J Med 278: 409-415, 1968

Effect of manipulating serum phosphorus with phosphate binder on circulating PTH and FGF23 in renal failure rats



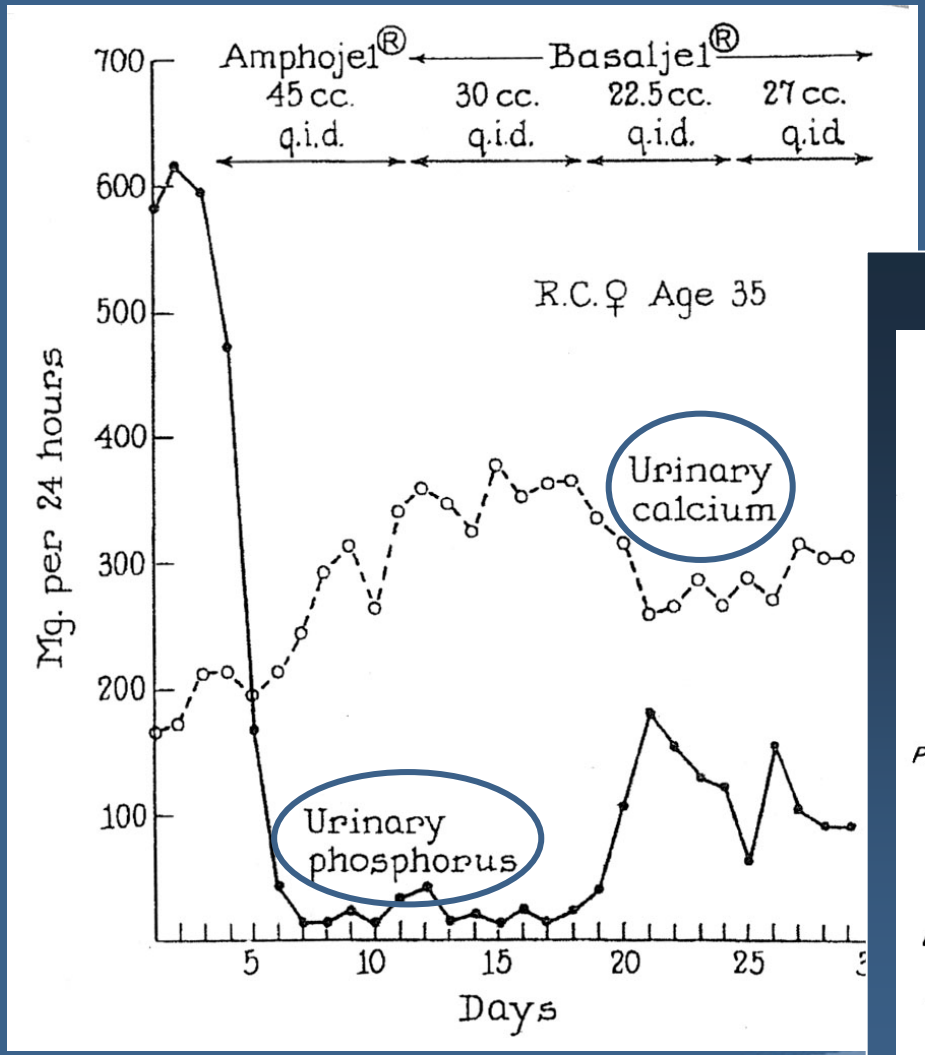


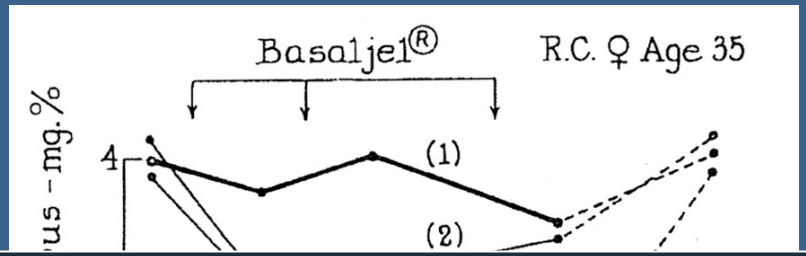


Nagano N et al:
Kidney Int
69: 531-537, 2006

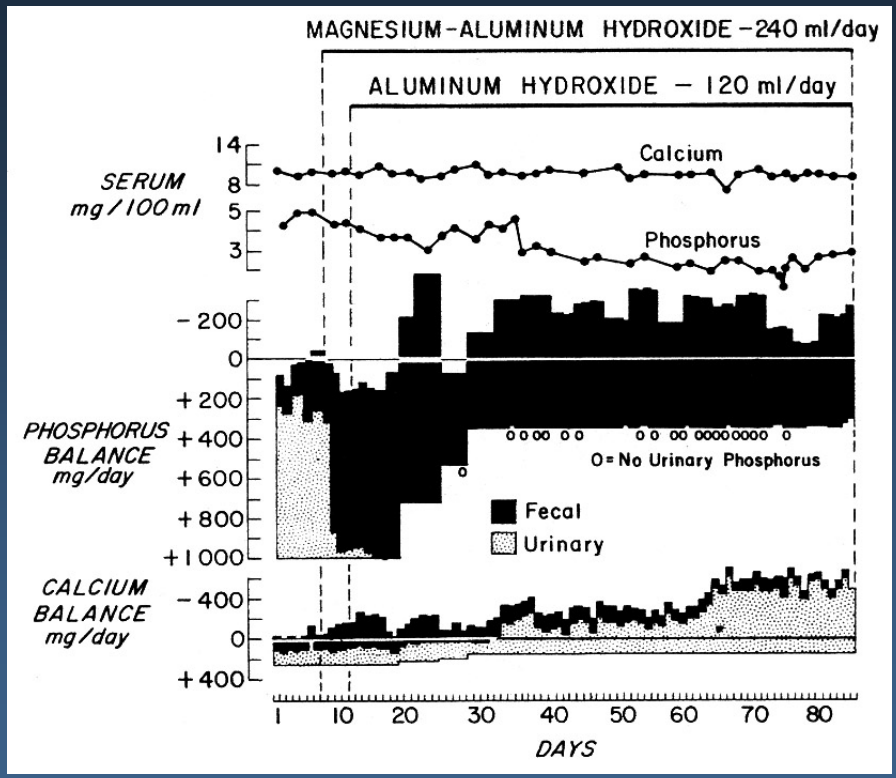
Effects of (a) continuous and (b) intermittent treatment with sevelamer on serum phosphorus (left) and calcium (right) levels

Aluminum gels in the management of renal phosphatic calculi





Gastrointestinal Ca absorption ↑ ($^{47}CaCl_2$)



Lotz M et al: New Engl J Med 278: 409-415, 1968

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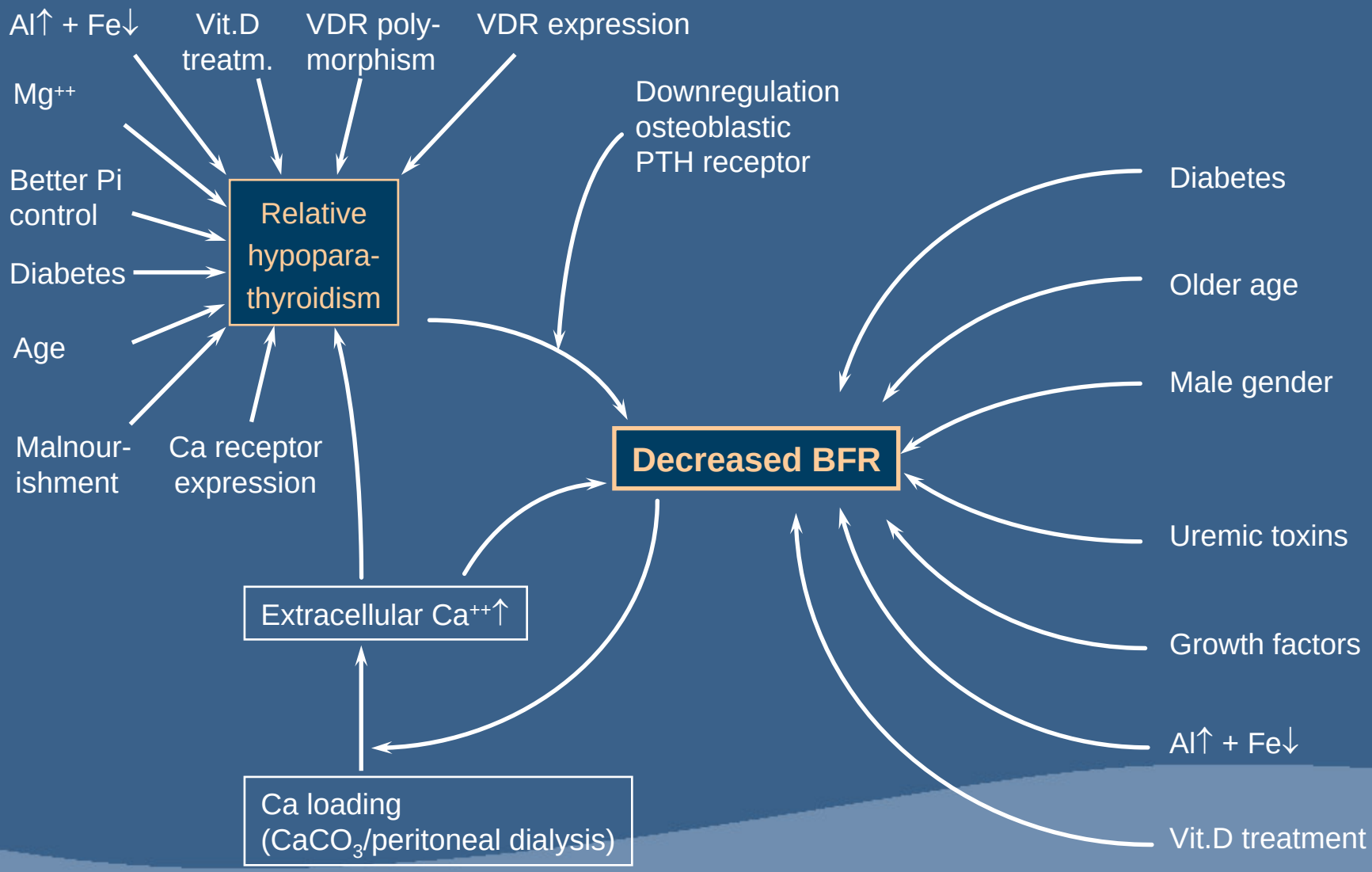
Calcium in blood, normal value: 2.2-2.7 mmol/l
4.5-5 meq/L
9.0-10.5 mg/l

- Ionized or free calcium : 48%
- Calcium bound to albumin : 40%
- Calcium bound to various anions
  - phosphate
  - lactate
  - citrate
  - bicarbonate 12%
- Ionized Calcium to be determined within 2hrs or 6hrs if stored at 4°C
- Lehman et al Am. J. Dis. Chid. 143 / 1340 / 1989
  Inverse relationship between ionized calcium and phosphate at all pH levels, counter ion effect.

Adynamic Bone Disease



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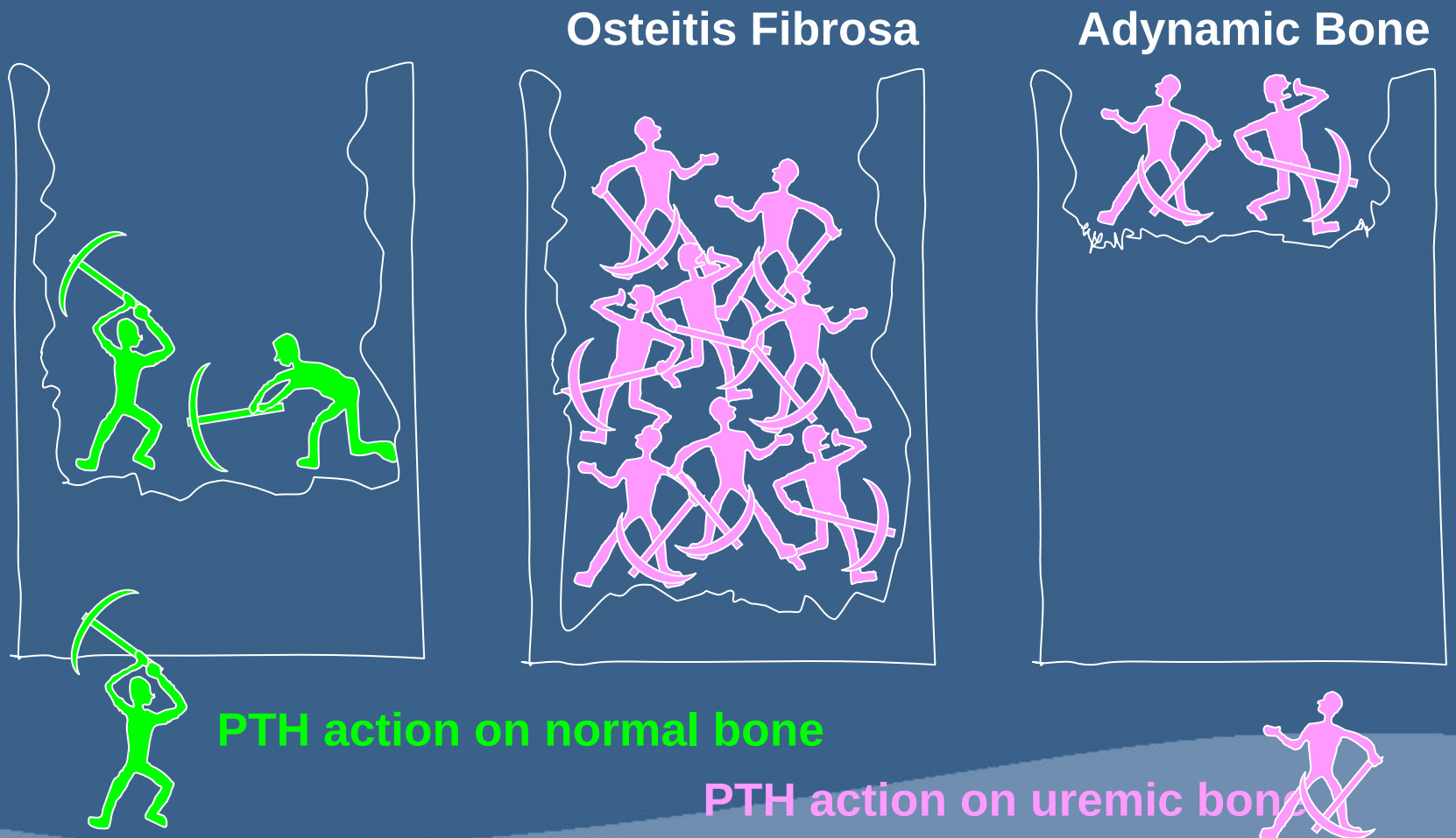
Couttenye MM et al: Kidney Int 56, S70, 1999

Increased Skeletal Resistance to PTH in Uremia



From M. Fukagawa, Kobe, Japan

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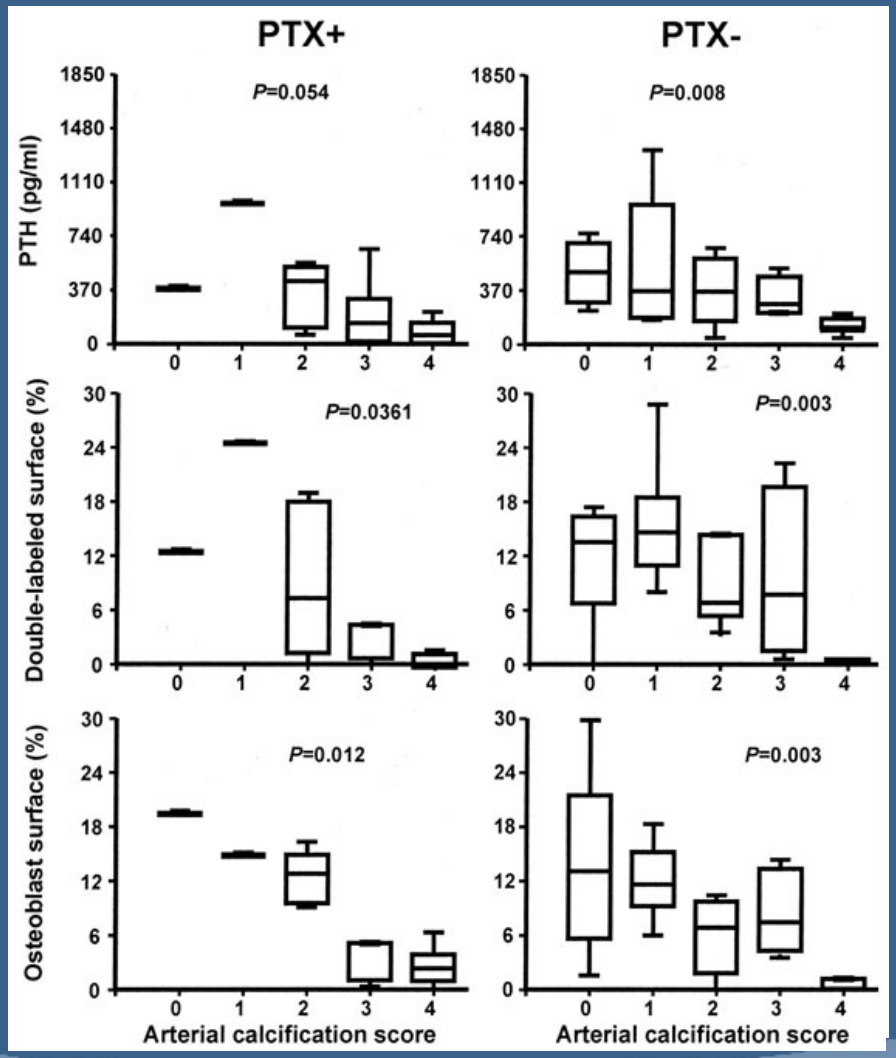
Arterial calcifications and bone histomorphometry in ESRD

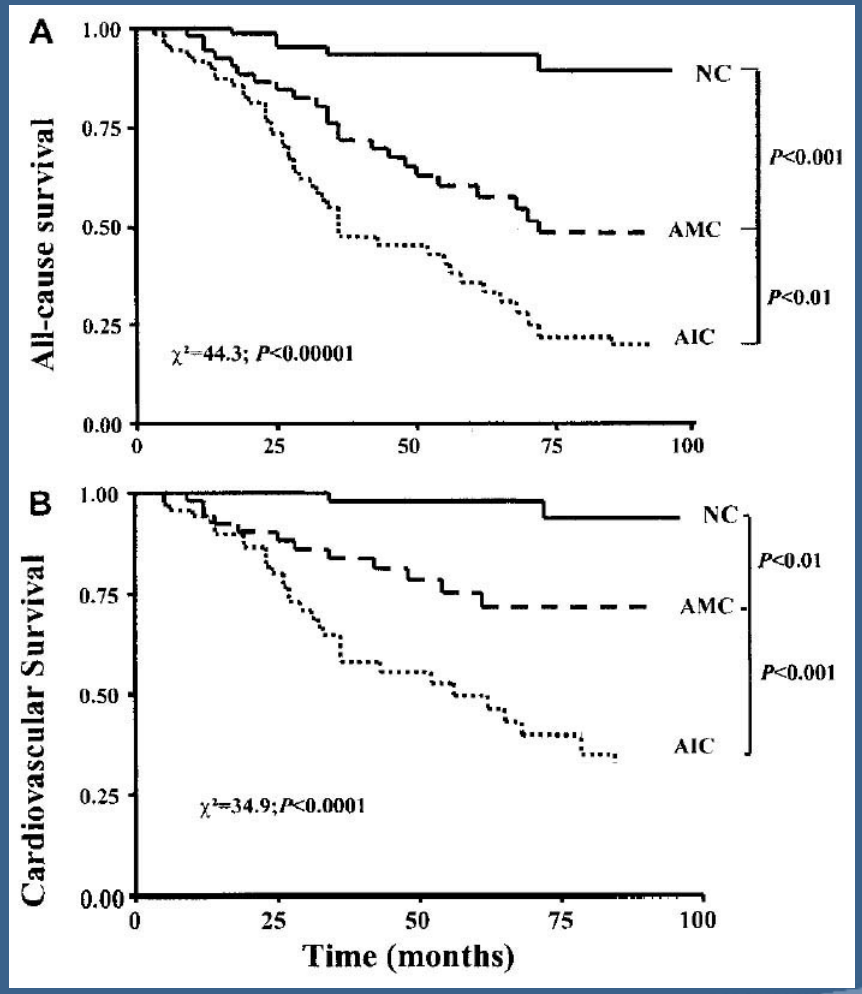


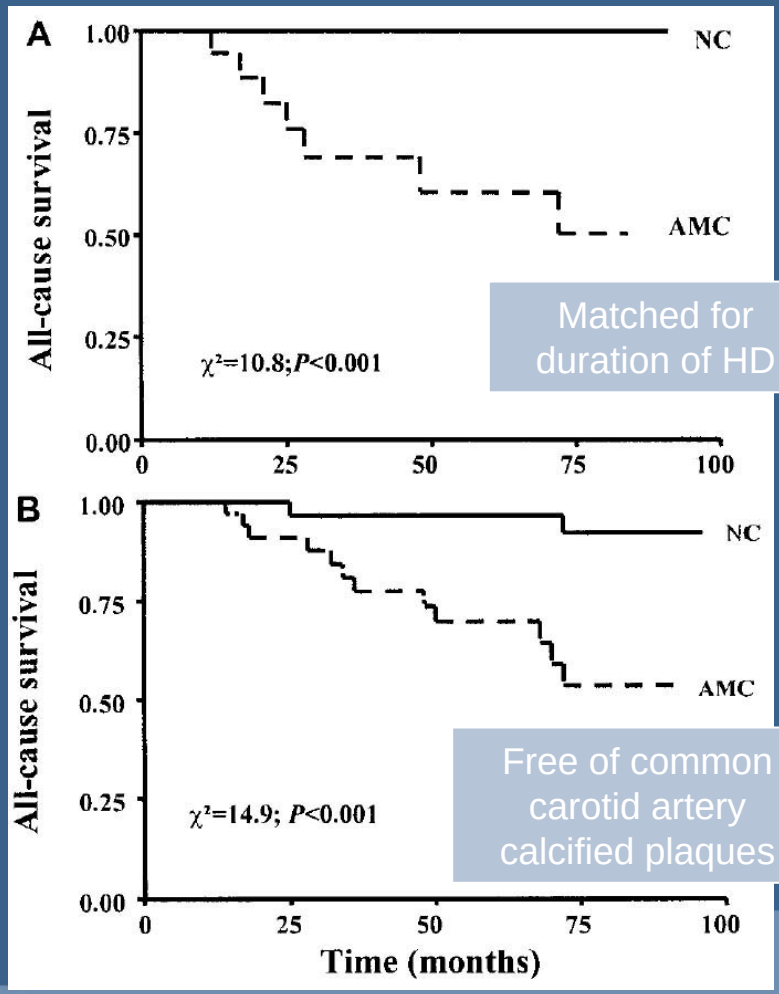
Therapeutic interventions associated with excessive lowering of parathyroid activity (parathyroidectomy, excessive calcium or aluminum load) **favor lower bone turnover and adynamic bone disease,** which could influence the **development and progression of arterial calcification.**

London GM et al, JASN 15: 1943-1951, 2004

Arterial media calcification in ESRD: impact on all-cause and cardiovascular mortality

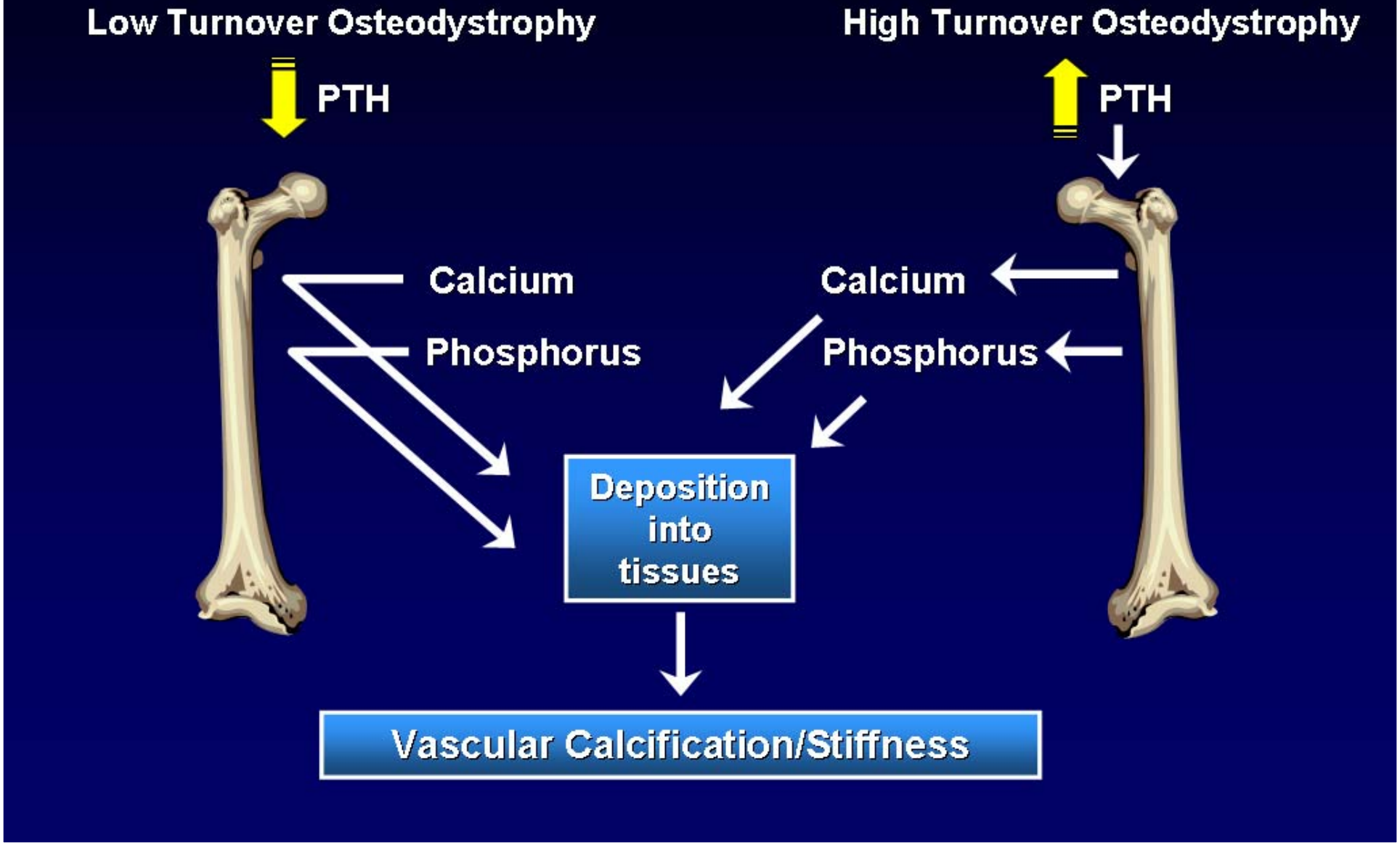
NC no calcification
AMC Arterial media calcification
AIC Arterial intima calcification





London GM et al: Nephrol Dial Transplant 18: 1731-1740, 2003

Both Forms of Osteodystrophy in CKD Contribute to Hyperphosphatemia



CALCIUM LOAD in DIALYSIS PATIENTS

- Increase in serum calcium –ionized calcium
- Decrease in PTH secretion ,relative hypoparathyroidism
- Low bone turn over
- Less incorporation of calcium in bone
- Higher risk for development of vascular calcifications

EFFICIENT PHOSPHATE BINDING

AVOID EXCESIVE CALCIUM LOAD

Universiteit Antwerpen

Kidney Bone Disease

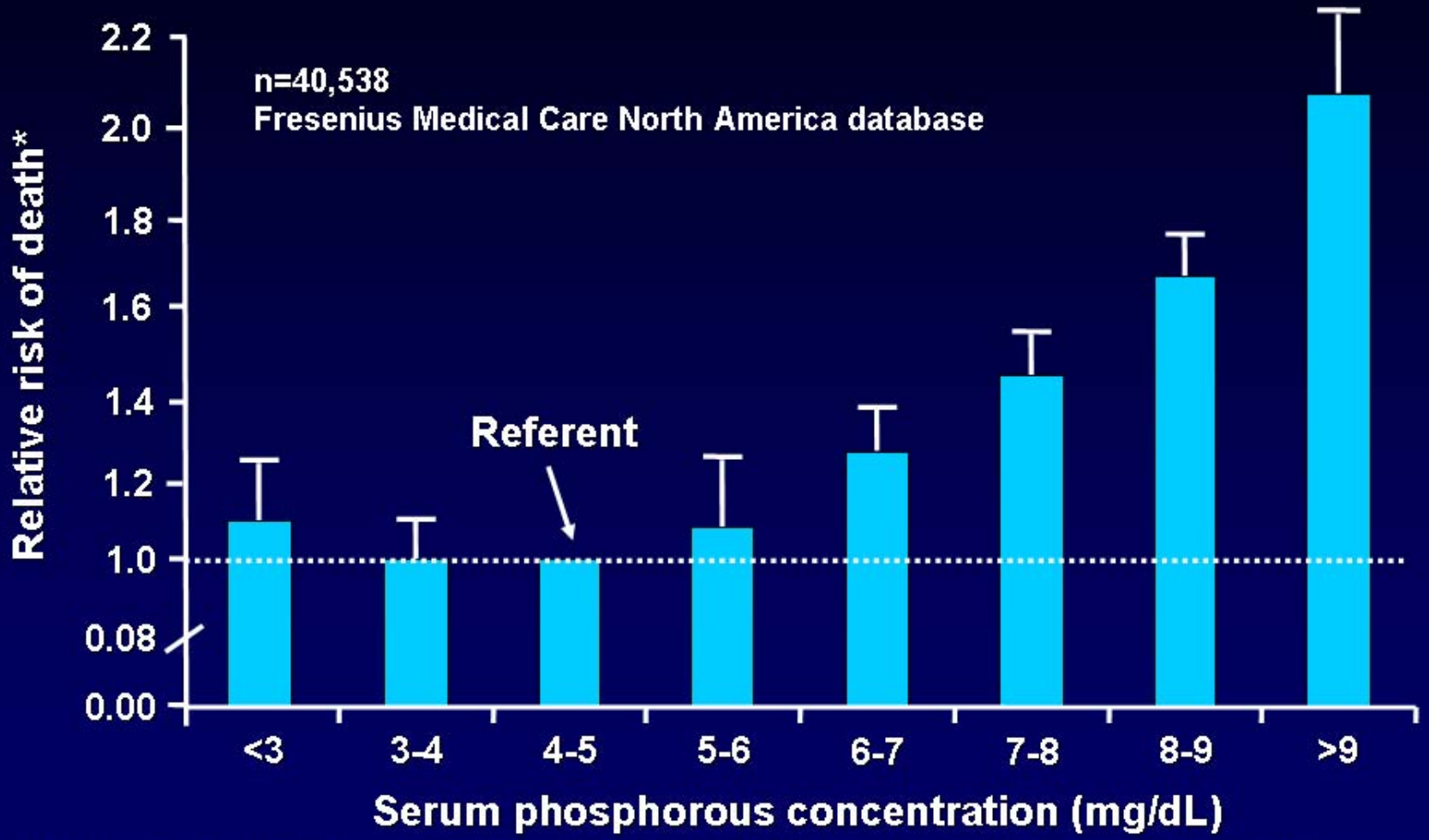
What happens when the kidney fails?

- ✓ Progression of kidney damage >> mineral metabolism
- ✓ Bone histology in ESRF
- ✓ Concept of calcium loading in CKD
- ➢ Non-calcium containing phosphate binders
  - o Lanthanum: a safe phosphate binder?
  - o Lanthanum and the calcium loading concept

M.E. De Broe
Stockholm
31 March 2009

Universiteit Antwerpen

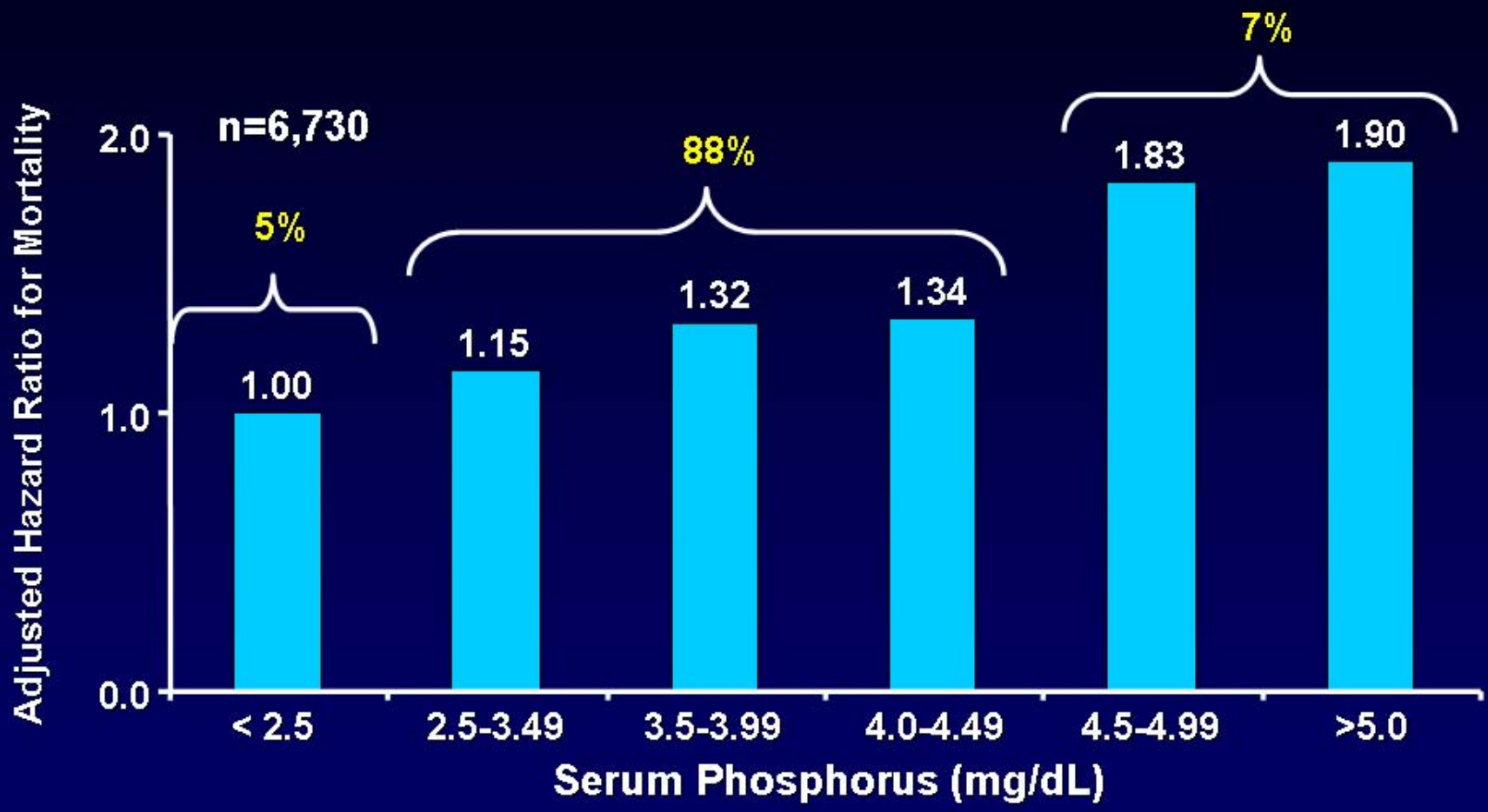
Serum Phosphorus and Mortality Risk in CKD Patients on Dialysis



*Multivariable adjusted for age, gender, race, diabetes, dialysis vintage, body weight, urea reduction ratio, serum albumin, creatinine, predialysis blood urea nitrogen, bicarbonate, cholesterol, hemoglobin, ferritin, and aluminum.

Block GA et al. *J Am Soc Nephrol.* 2004;15:2208.

Serum Phosphorus and Mortality Risk in CKD Patients Not on Dialysis



*Adjusted for baseline age, sex, race, cerebrovascular disease, diabetes, ischemic heart disease, HF, acute renal failure, calcium intake from medications, serum calcium, inverse of baseline creatinine, time-averaged creatinine, slope of creatinine, maximal creatinine concentration, hemoglobin. CKD (CrCl 50.4 – 39.5 mL/min)

Kestenbaum B. *J Am Soc Nephrol.* 2005;16:520.

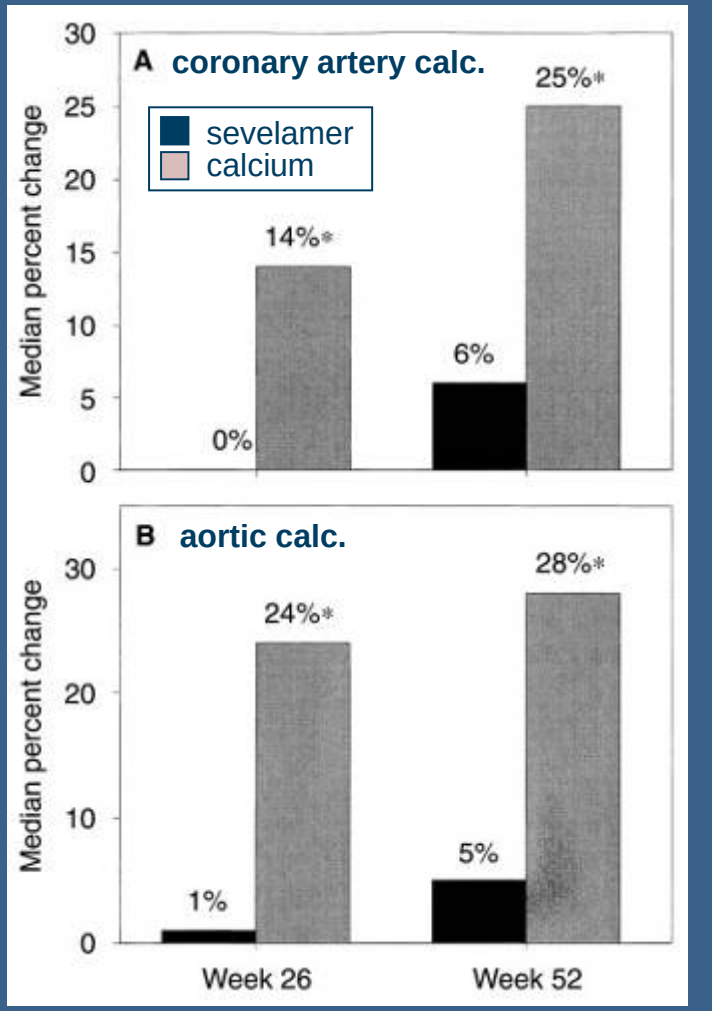
Traitement de l'Hyperphosphatémie chez le Patient Dialysé. Les Chélateurs Intestinaux du Phosphore

Evolution du traitement médical de l'hyperphosphatémie

1966	Carbonate de calcium
1972	Hydroxyde d'alumine (1976 encéphalopathie)
1986	Carbonate de magnésium
1986	Alginate de calcium
1989	Acétate de calcium
1995	Chlorure de zirconyl
1996	Kétoglutarate de calcium
1999	Sulfate de fer hydrolysé
2000	Sevelamer
2001	Carbonate de lanthane
2003	Inhibiteurs du transport intest. du phosphate

Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients

Baseline characteristics	Sevelamer (N = 99)	Calcium (N = 101)	P value
Age *years* (mean ± SD)	57 ± 14	56 ± 16	0.88
Sex *% female*	36%	34%	0.77
Race			
Black	17%	23%	0.34
White	71%	66%	
Other	12%	11%	
Diabetes %	32%	33%	1.0
Hypertension %	86%	83%	0.70
Smoker %	3%	8%	0.21
Primary Cause of ESRD %			
Hypertension	16%	17%	0.66
Glomerulonephritis	26%	16%	
Diabetes	23%	28%	
Polycystic kidney disease	9%	11%	
Other	26%	28%	
Dialysis vintage *years, median*	3.6	2.9	0.24
Phosphate binder use prior to study entry %			0.81
Calcium carbonate	38%	44%	
Calcium acetate	33%	36%	
Calcium + aluminum	14%	13%	
Sevelamer	3%	1%	
Other combinations	12%	6%	
Vitamin D usage at study entry	56%	59%	0.67



Change in calcification scores from baseline to weeks 26 and 52 in pt with score>30 at baseline

Compared with calcium-based phosphate binders, sevelamer is less likely to cause hypercalcemia, low levels of PTH, and progressive coronary and aortic calcification in hemodialysis patients

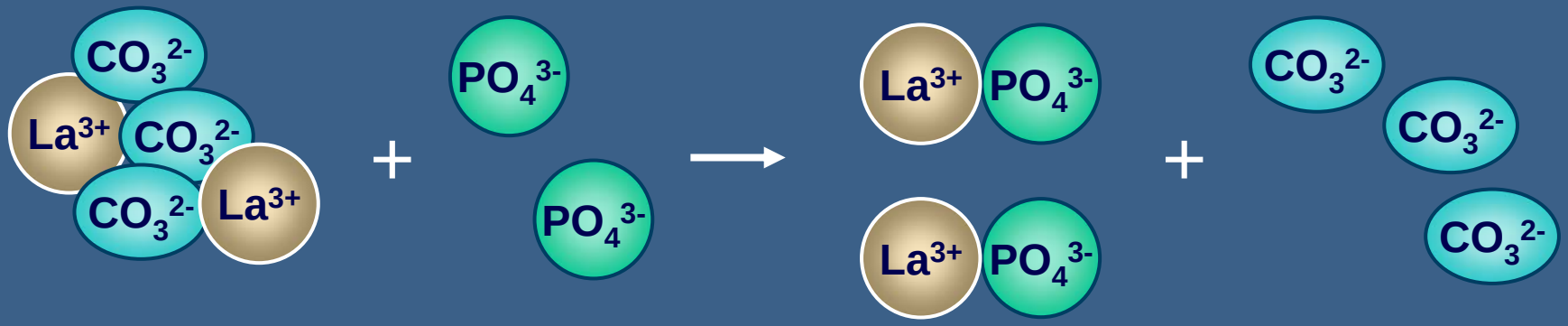
Chertow GM et al:
Kidney Int 62: 245-252, 2002

Lanthanum carbonate as a phosphate binder

Lanthanum: the element

- MW: 139 Da (2 stable isotopes)
- Silvery white, malleable, ductile rare earth element; occurring at varying concentrations in terrestrial crust and surface water.

- ***Tri-valent hard acid cation → high affinity for phosphate***



$Ks = [La^{3+}][PO_4^{3-}] = 7.08 \times 10^{-27}$

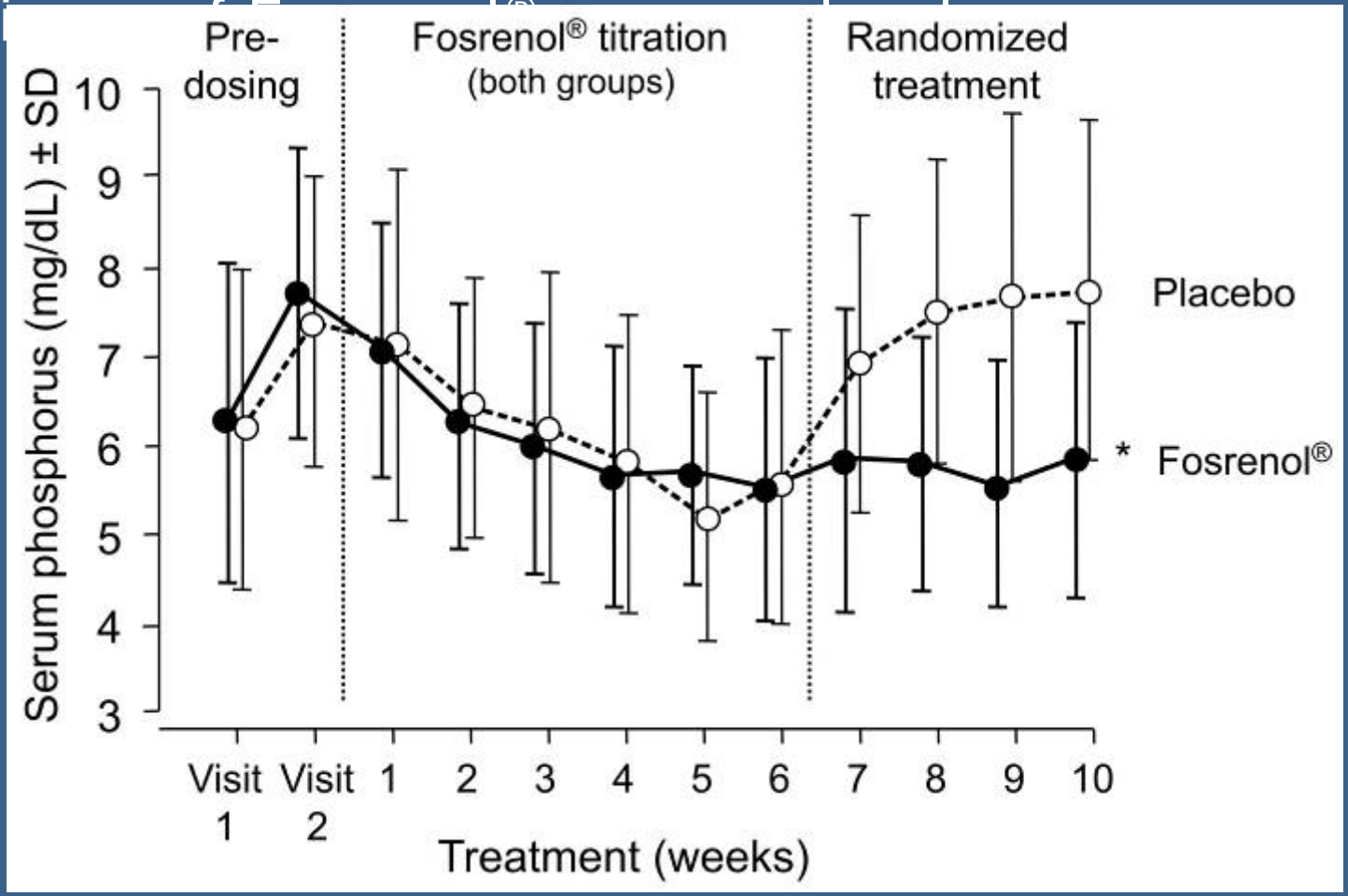
= solubility constant

Patient Exposure to Fosrenol®

- Extensively studied phosphate binder at launch
  - Over 5500 patients with clinical evaluation
- Market experience in the USA since January 2005 and in
  the EU since 2006
  - Over 100,000 patients treated
- Through extended treatment, some 28 patients have now receivedFosrenol® for 5 years or more, 22 on 6th year of treatment.

Shire data on file

Effi

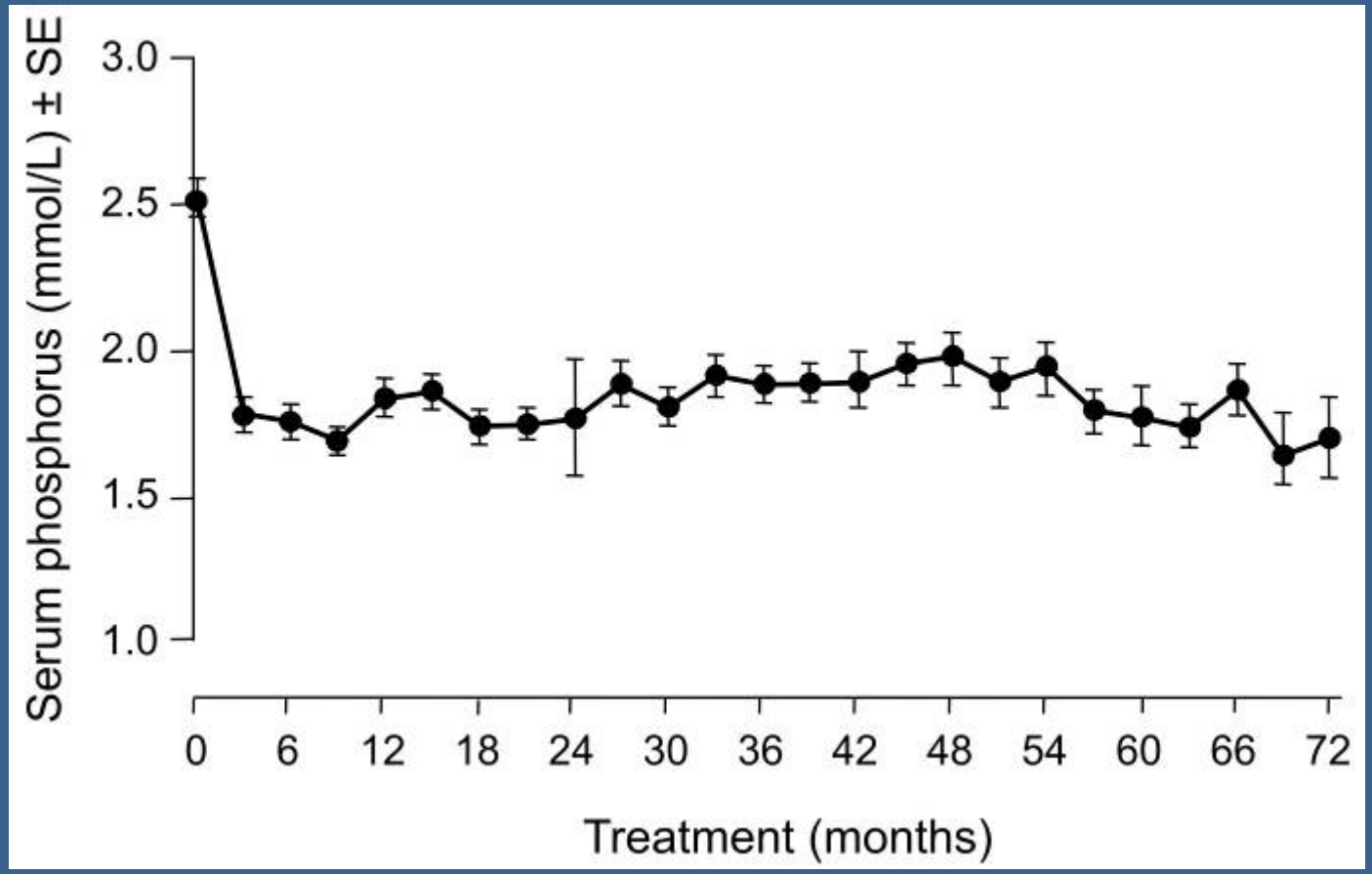


* *P* < 0.0001 between treatment groups at endpoint

1.0 mmol/L = 3.1 mg/dL

Adapted from: Joy MS, Finn WF. *Am J Kidney Dis* 2003;42:96–107

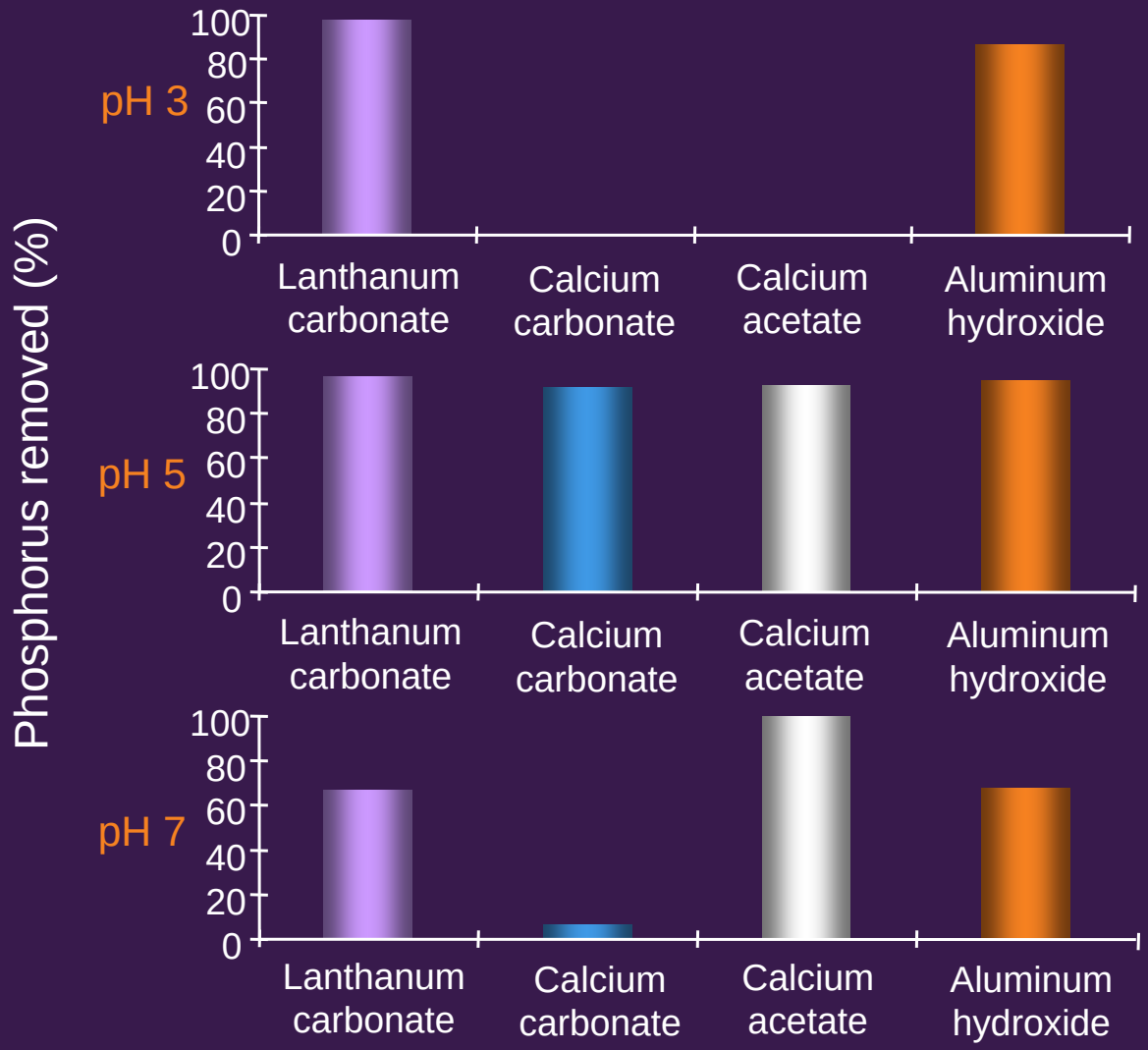
Efficacy of Fosrenol®: long term



1.0 mmol/L = 3.1 mg/dL

Adapted from Hutchison A *et al*. Poster presented at ASN 2005

High phosphate-binding affinity *in vitro:* independent of pH

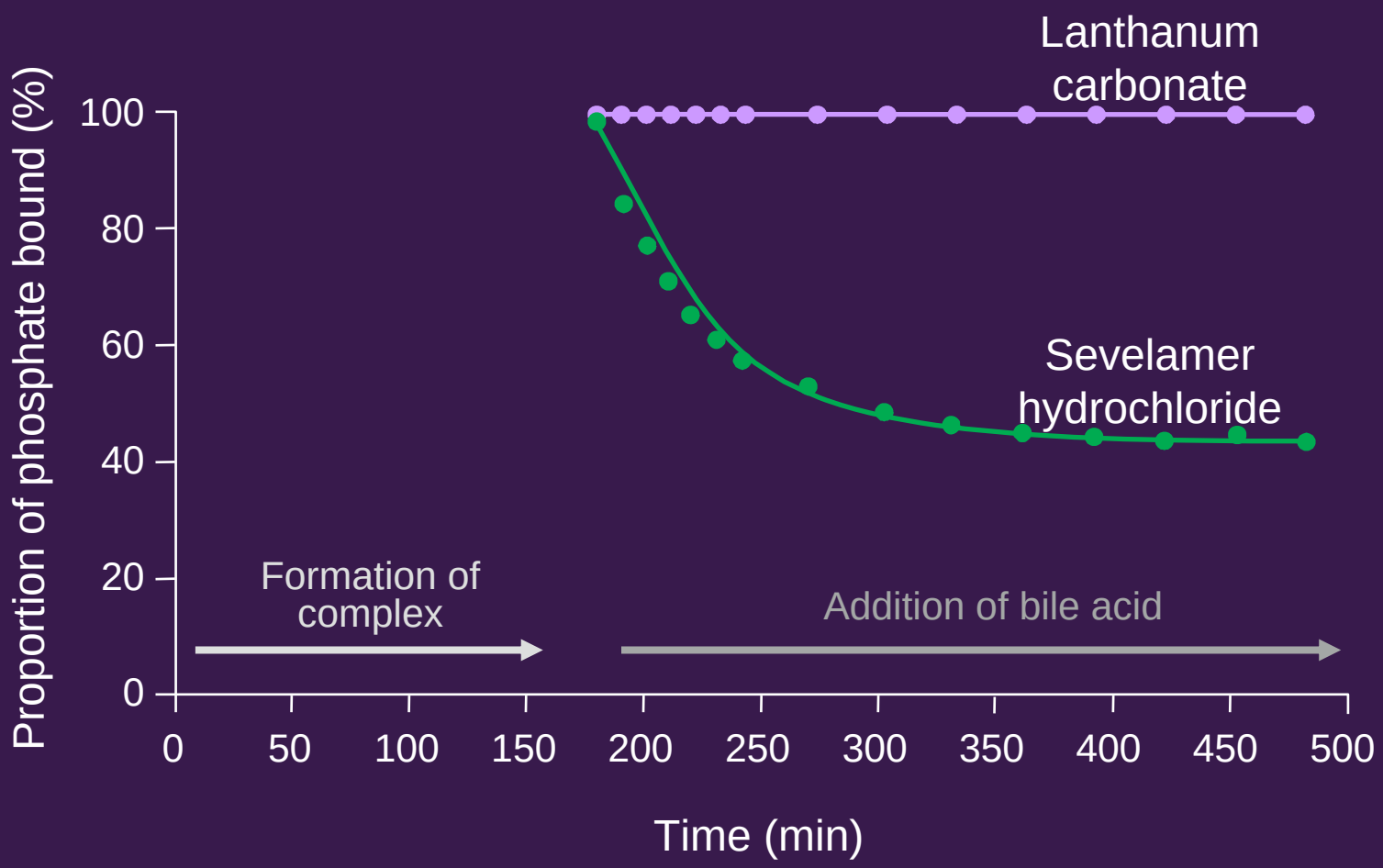


Lanthanum carbonate binds phosphate across a wide pH range

Similar affinity to aluminium hydroxide

Adapted from: Damment SJP, Webster I. Poster presented at ASN 2003

Selective phosphate binding: no displacement by bile acids



Adapted from: Autissier V *et al*. Poster presented at ASN 2005

Lanthanum carbonate as a phosphate binder

Summary of randomised studies

Overall, randomised studies (USA, Europe, Taiwan) confirm that:

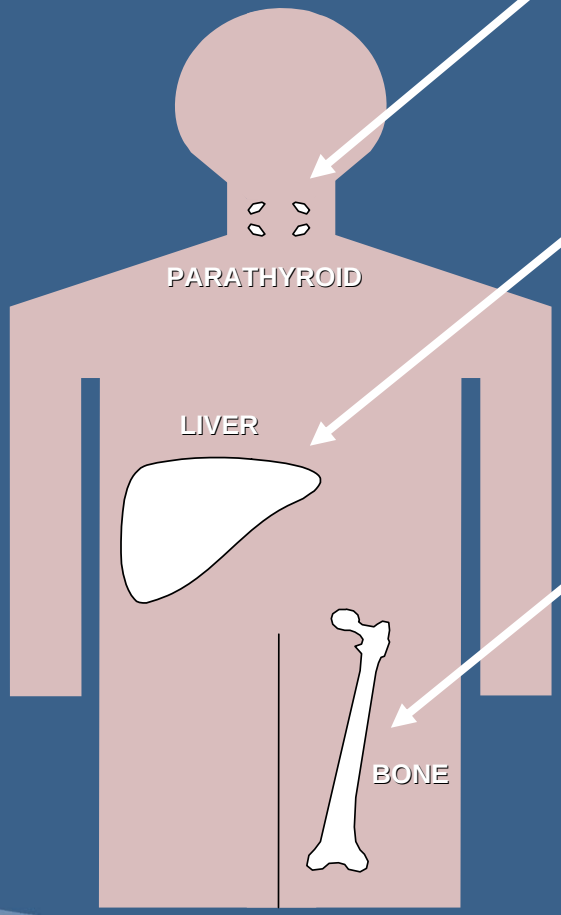
- **Lanthanum carbonate is a consistently effective binder of dietary phosphate**
- **Doses up to 3000 mg/day reduce serum phosphate to target levels in the majority of patients**
- **Maintenance of target phosphate levels is similar between lanthanum carbonate and standard therapy**
- **Phosphate levels are controlled in long-term use (up to 154 weeks of treatment)**

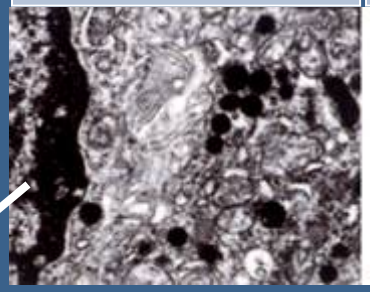
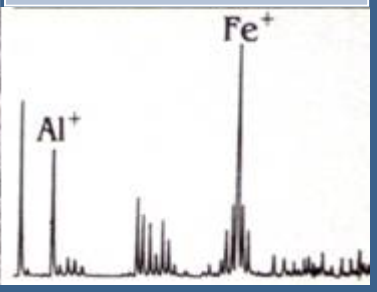
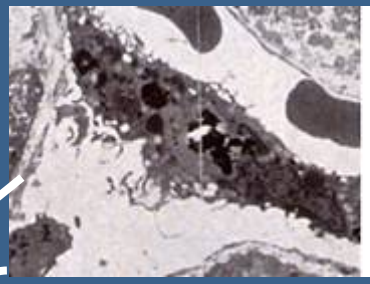
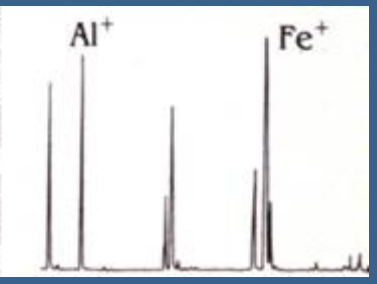
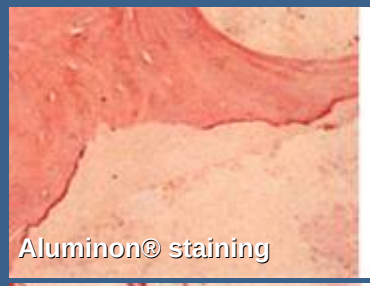
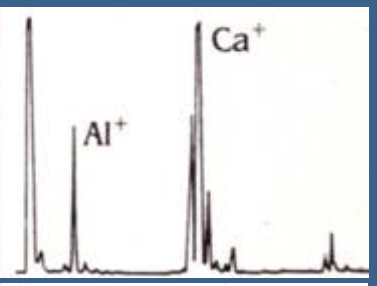
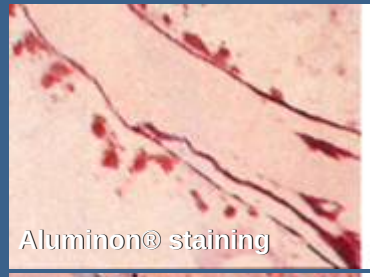
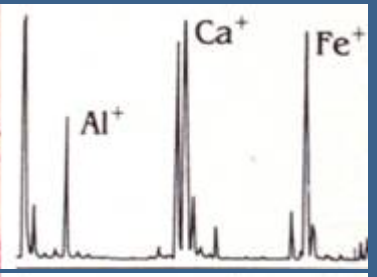
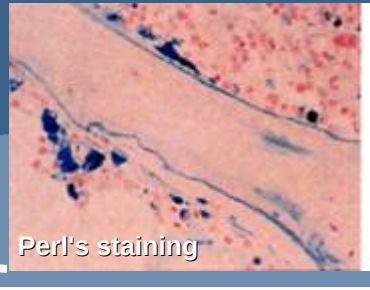
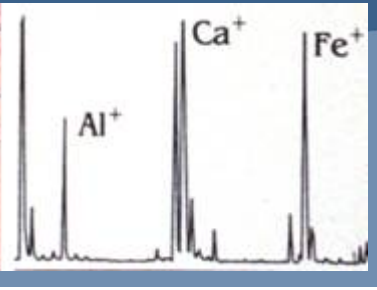
Hutchison AJ et al: Nephrol Dial Transplant 19: 1902-1906, 2004

Joy MS et al: Am J Kidney Dis 42: 96-107, 2003

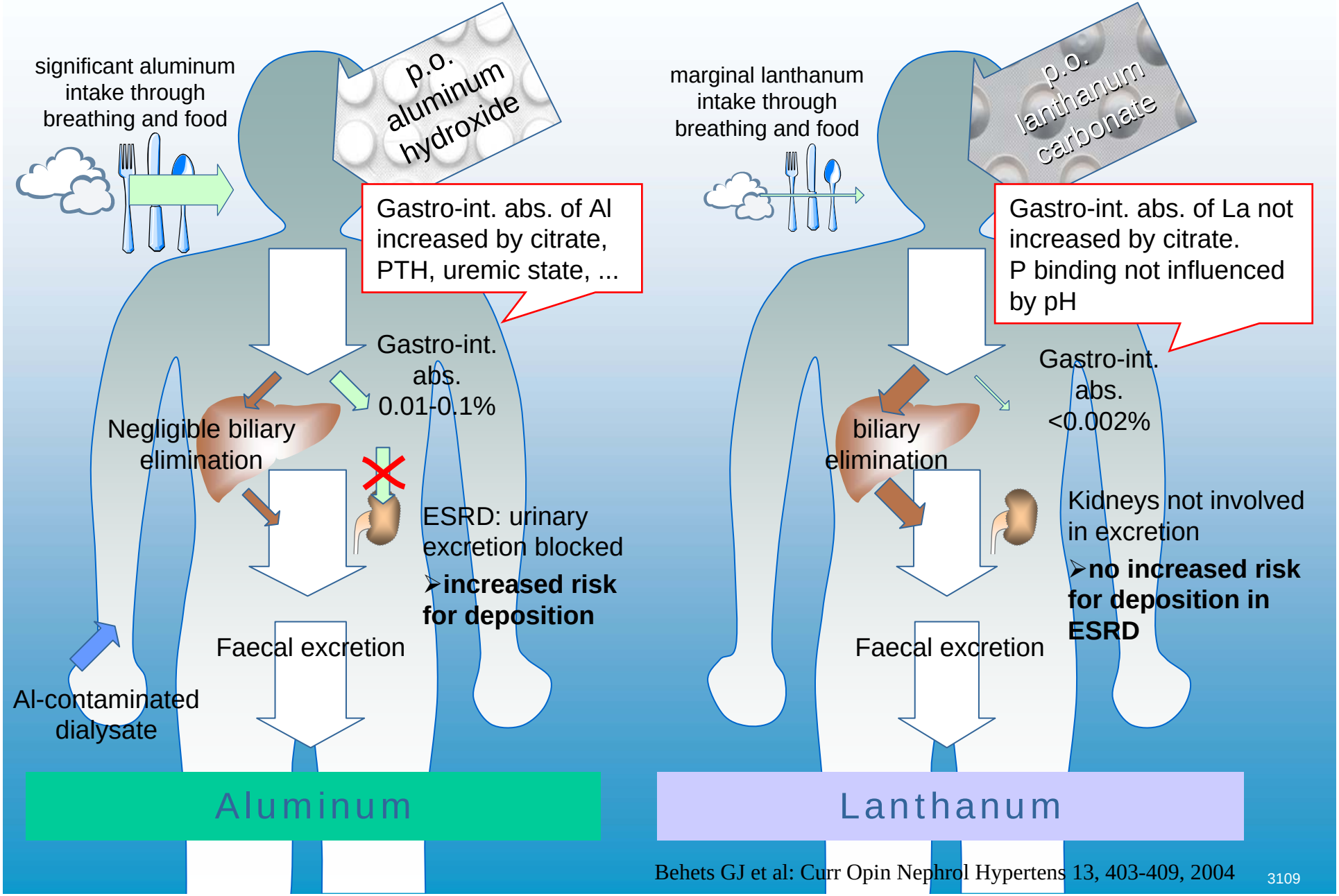
Hutchison AJ. Nephron Clin Pract 100: c8–19, 2005

Ultrastructural localisation of aluminum



MICROSCOPIC	LAMMA	
		secretory granules
		lysosomes
		
		mineralisation front
		

Metabolism of two trivalent cations: *Aluminum - Lanthanum*

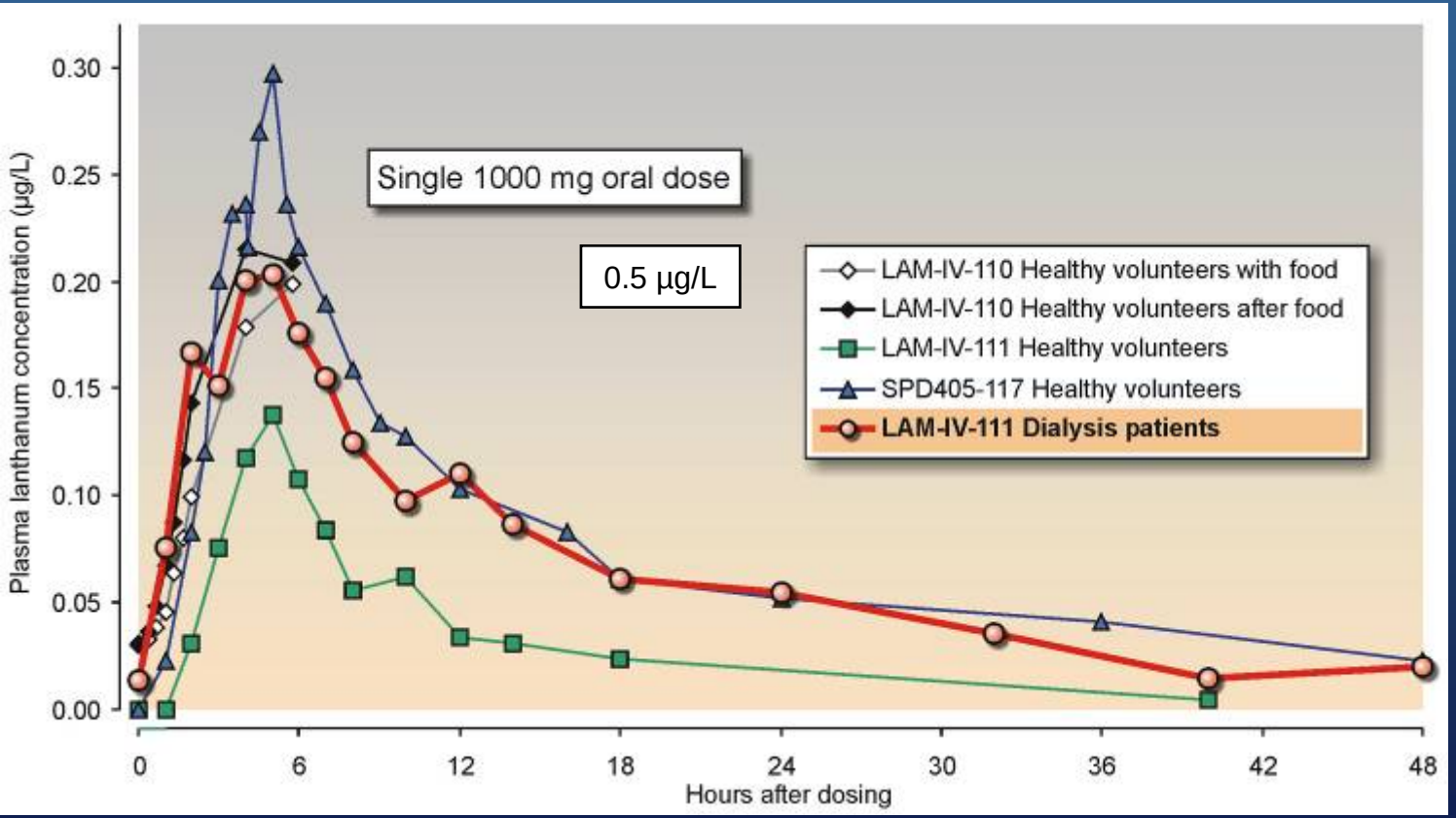


Behets GJ et al: Curr Opin Nephrol Hypertens 13, 403-409, 2004

Lanthanum carbonate as a phosphate binder

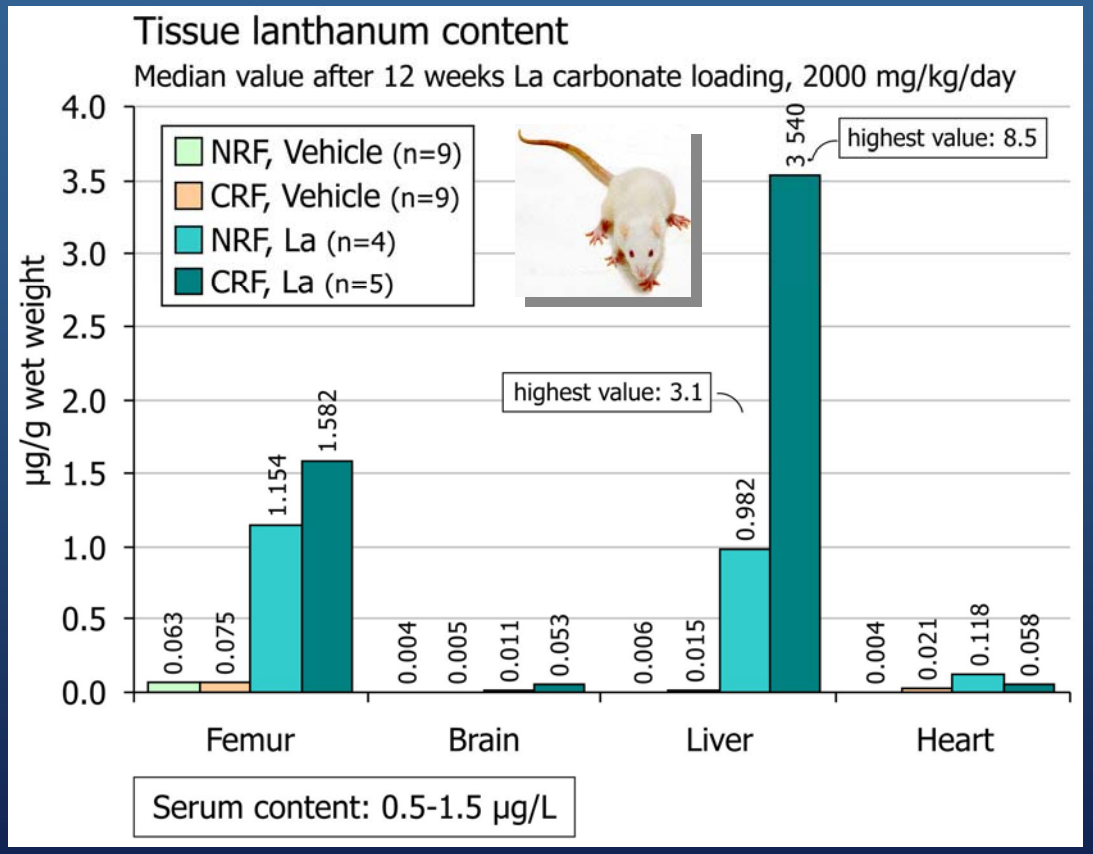
Lanthanum Pharmacokinetics

Healthy subjects vs dialysis patients



D'Haese PC et al: Kidney Int 68: 2906-2910, 2005

Tissue deposition of lanthanum



Behets G et al

Tissue deposition of aluminum

Toxicity of aluminum is determined by its localization

Tissue Aluminum Levels and Toxicity

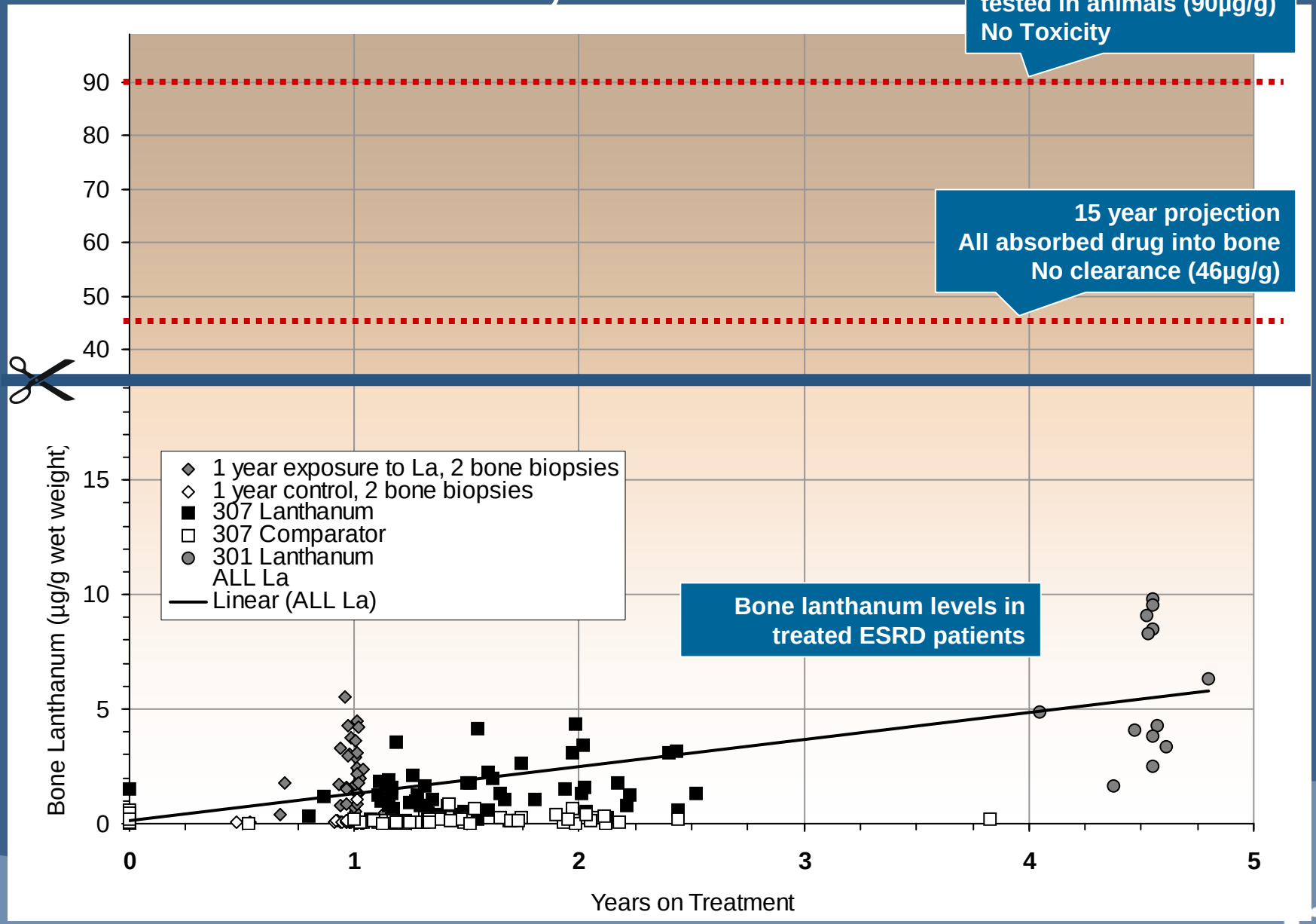
Tissue	Level	Localization	Toxicity
Bone	high	Min. front*	established
Brain	low	?	established
Liver	high	lysosomes	absent
Parathyroid	relatively low	secretory granules lysosomes	interference with the PTH release

Verbueken AH et al: Clin Chem 30, 764, 1984
D'Haese PC: PhD thesis, Univ. of Antwerp, 1988

Where is lanthanum localized?

Lanthanum carbonate as a phosphate binder

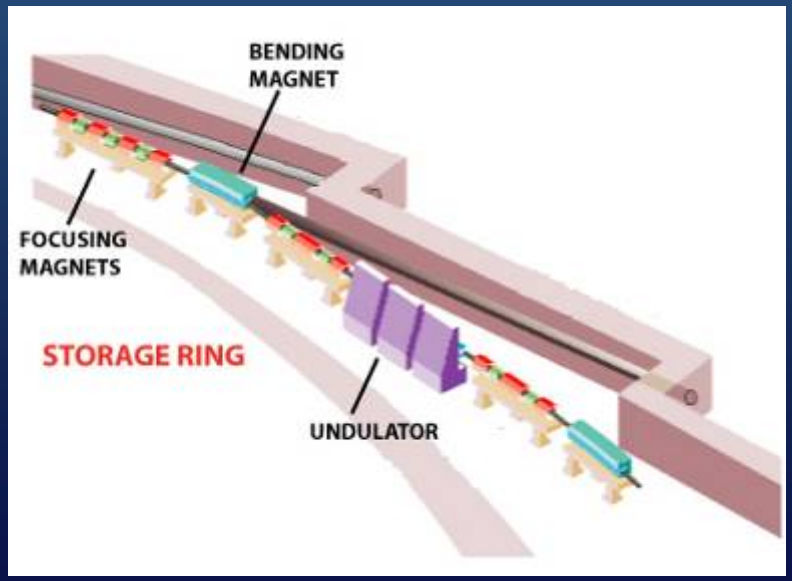
No evidence of toxicity



Damment SJ & Shen V: Clin Nephrol 67: 127-137, 2005

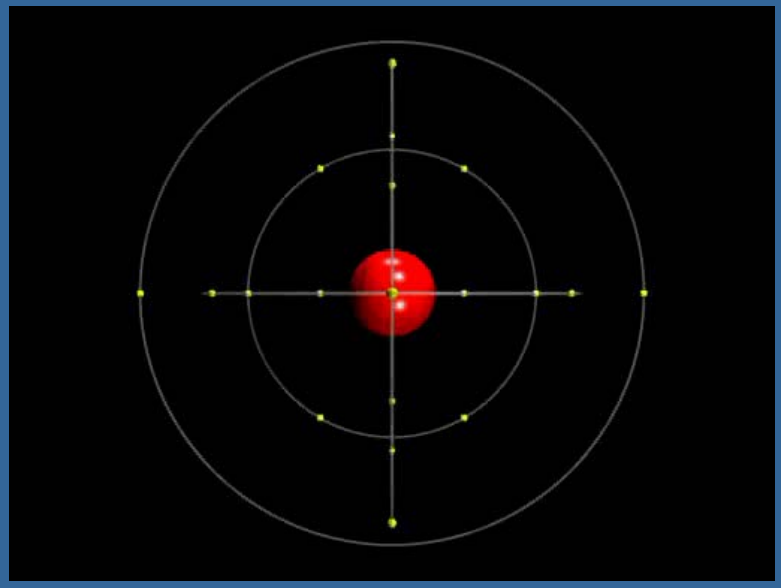
Deposition of lanthanum in bone

Extremely low La levels require sensitive detection methods

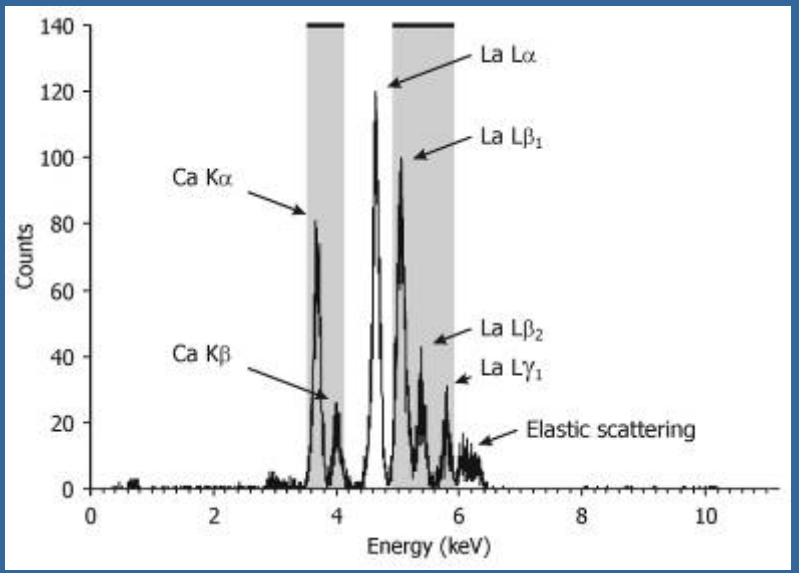


ESRF - The European Synchrotron Radiation Facility, Grenoble

Principle of X-ray fluorescence



Typical X-ray fluorescence spectrum of bone sample

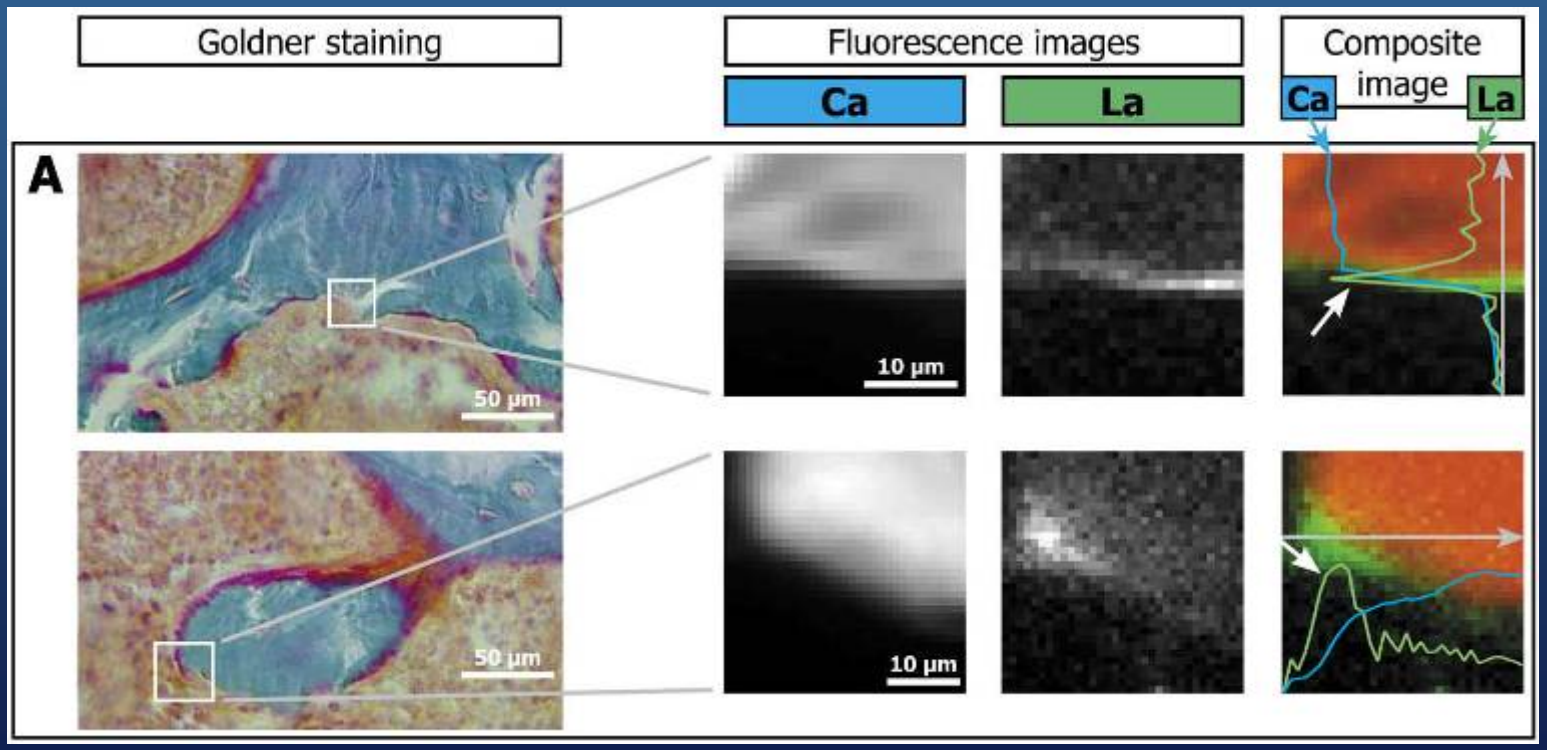


Behets GJ et al: Kidney Int 67: 1830-1836, 2005

Deposition of lanthanum in bone

Lanthanum is located at the outer edge of calcified bone

Normal bone



Rats loaded with 2000 mg/kg/day lanthanum carbonate for 12 weeks

Behets GJ et al: Kidney Int 67: 1830-1836, 2005

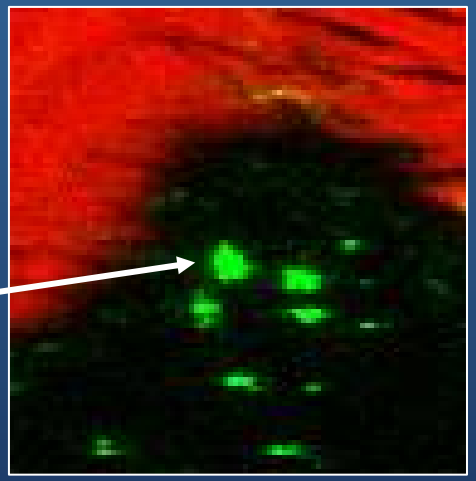
Deposition of lanthanum in bone

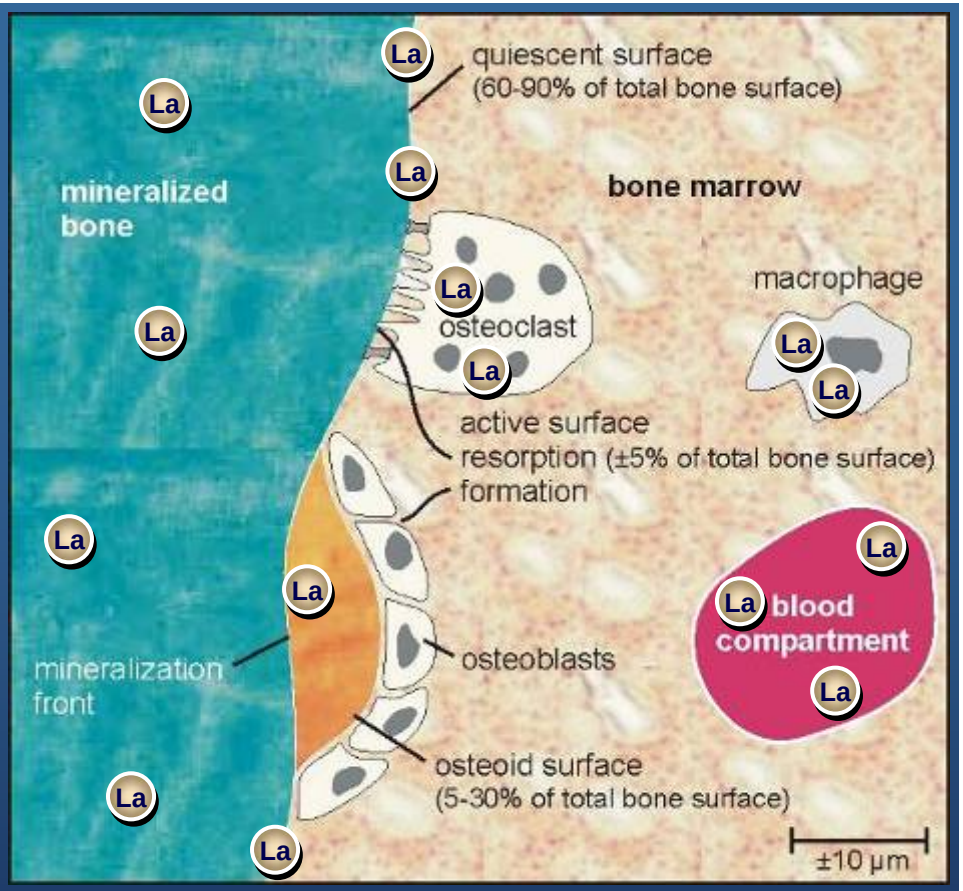
Different localisation of lanthanum in bone

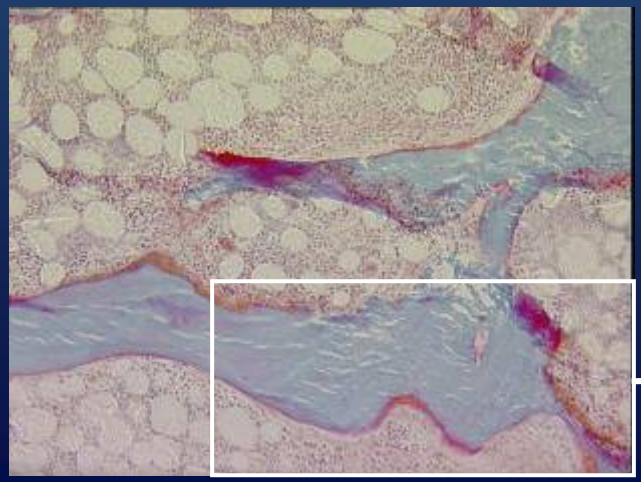
Patient 03/2493:

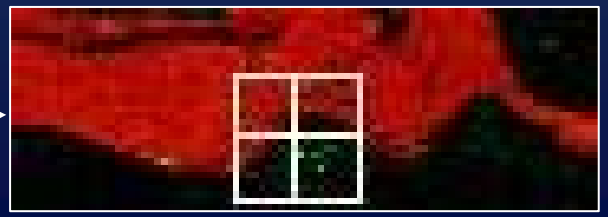
Treatment: 4 years
Bulk Bone La: ± 8 µg/g

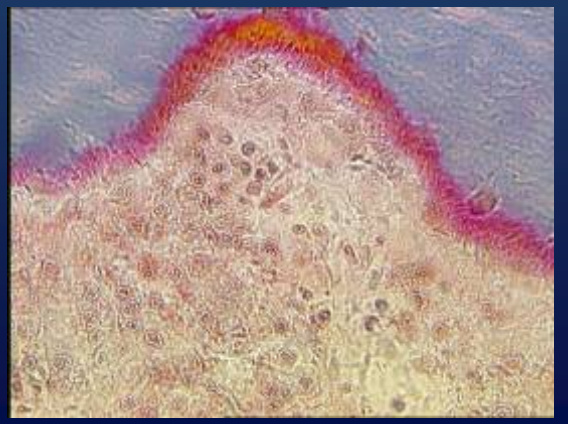
Fluorescence ratio
La/Ca: 0.01
La content:
0.099 mol%











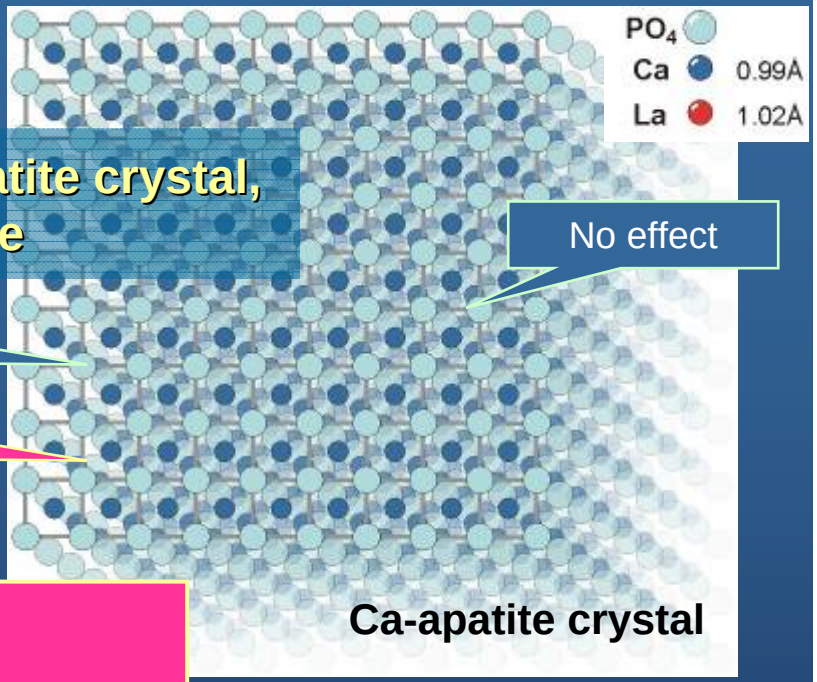
Behets GJ et al: Kidney Int 67: 1830-1836, 2005

Deposition of lanthanum in bone

Lanthanum is unlikely to interfere with Ca-apatite crystal, even when concentrated in 1% of bone volume

1 La / 50 000 Ca

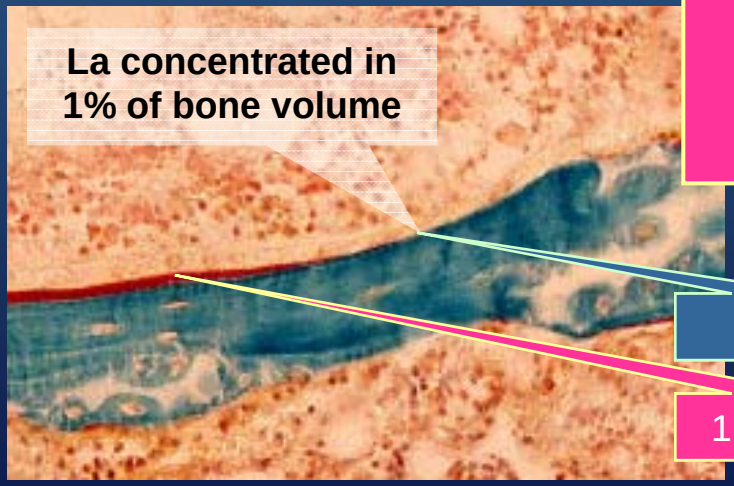
1 Al / 400 to 1600 Ca



Aluminum

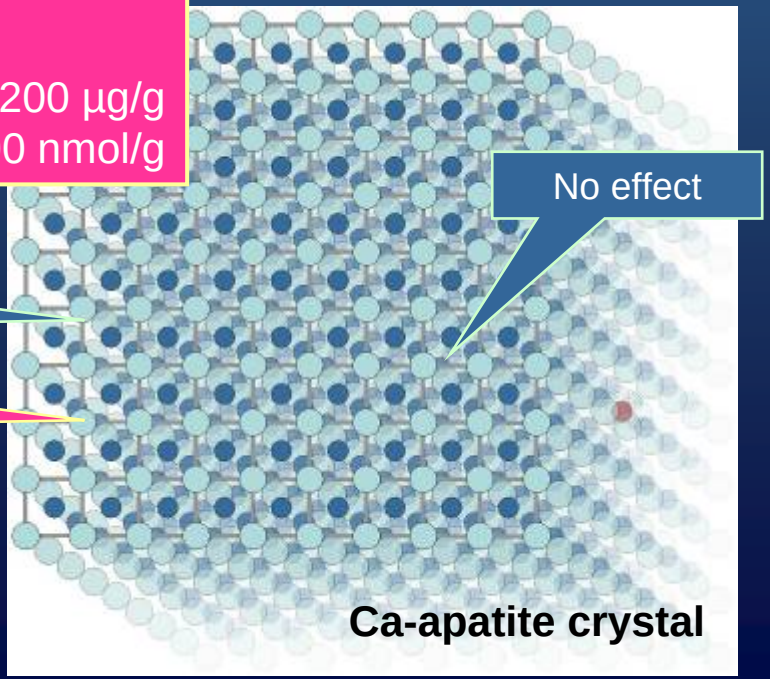
Mw: 27

Bone conc: 50-200 µg/g
= 1850-7400 nmol/g



1 La / 500 Ca

1 Al / 4 to 16 Ca



Maximal bone La concentration after 4 y: 10 µg/g
Molecular weight 139 Da 70nmol/gr

Lanthanum carbonate as a phosphate binder

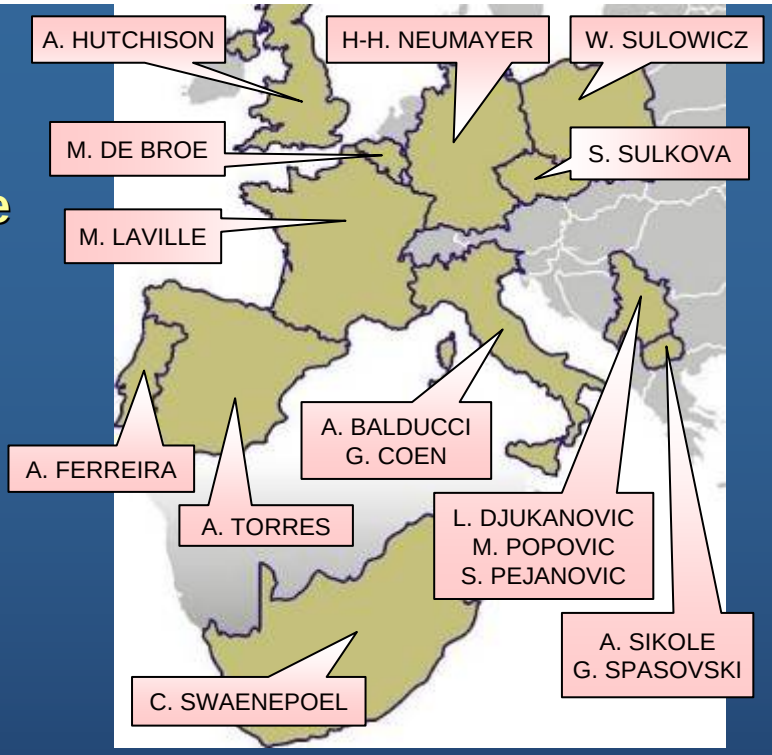
Open-label multicentre randomized prospective controlled study in dialysis patients

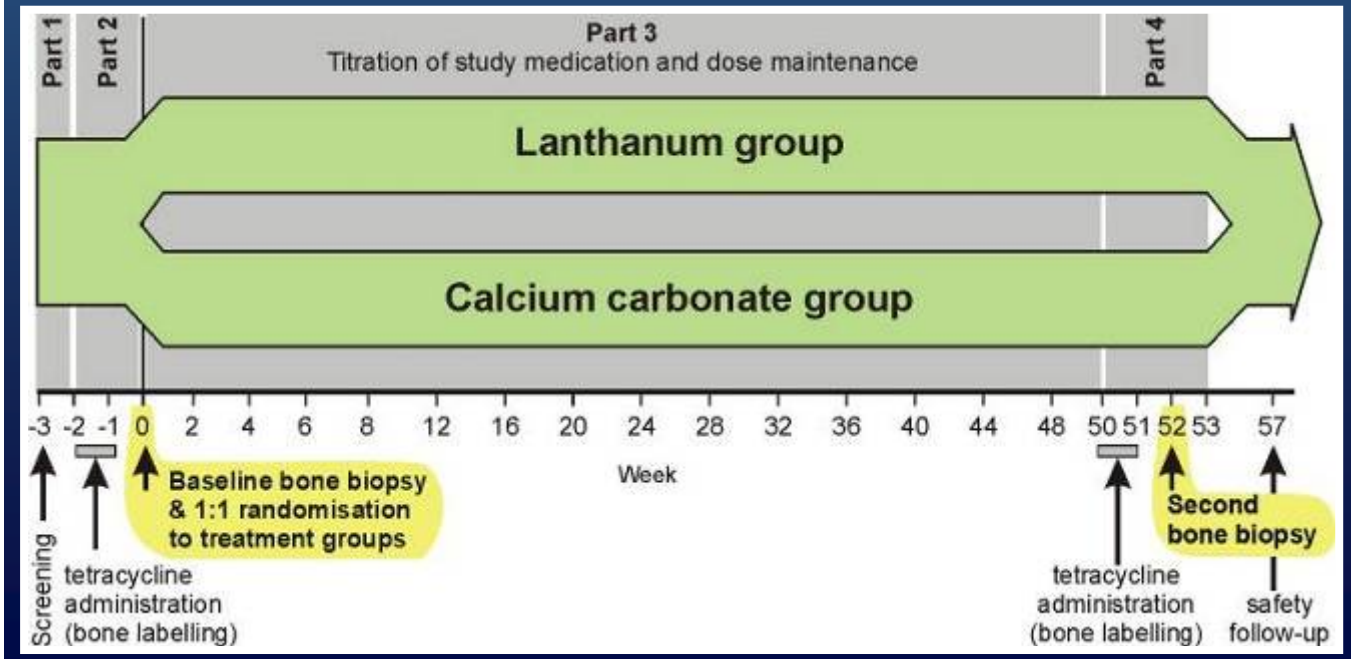
A total of 98 patients (age 55 ±14.3 y; 59 males) recruited from various dialysis centres in 12 countries.

In 63 of them a histomorphometric analysis of baseline *and* follow-up bone biopsies was performed.

Patients discontinued:

- Transplantation (n=10)
- Death (n=11)

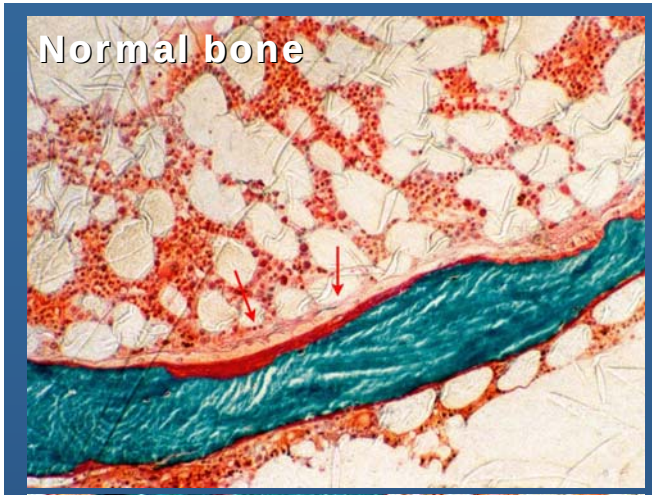


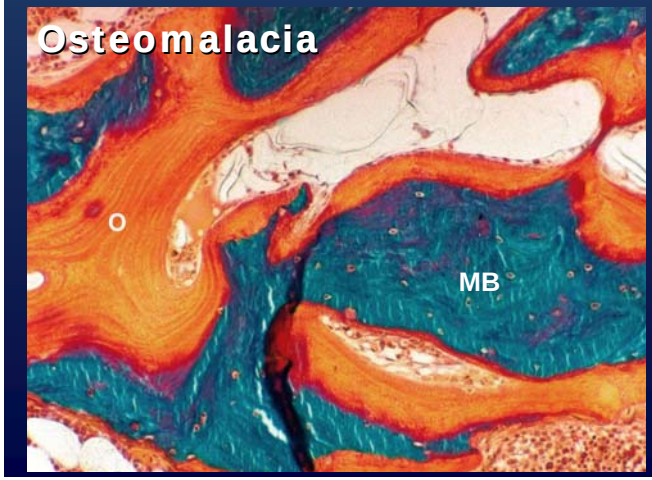


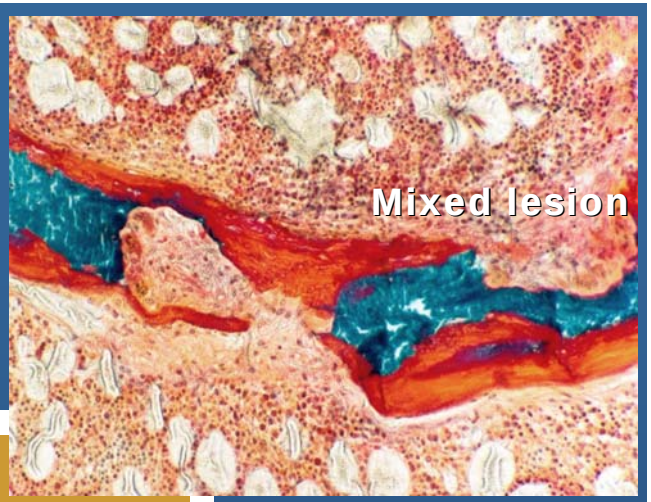
Maximal dose:
Lanthanum carbonate: 3750 mg/day
Calcium carbonate: 9000 mg/day

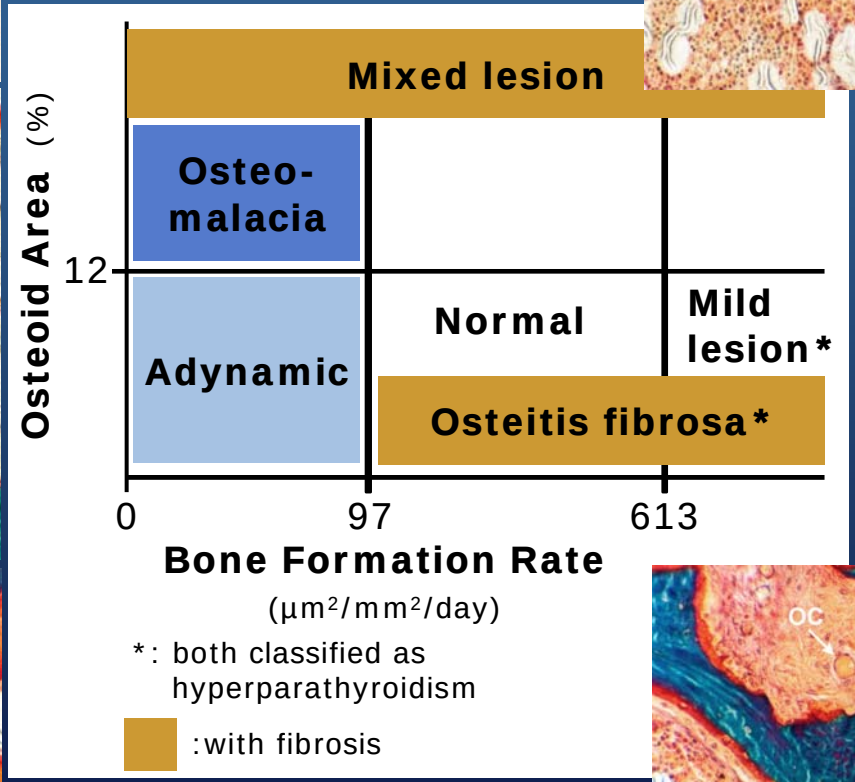
D'Haese PC et al:
Kidney Int 63 (S85): 73-78, 2003

Histologic classification of renal osteodystrophy

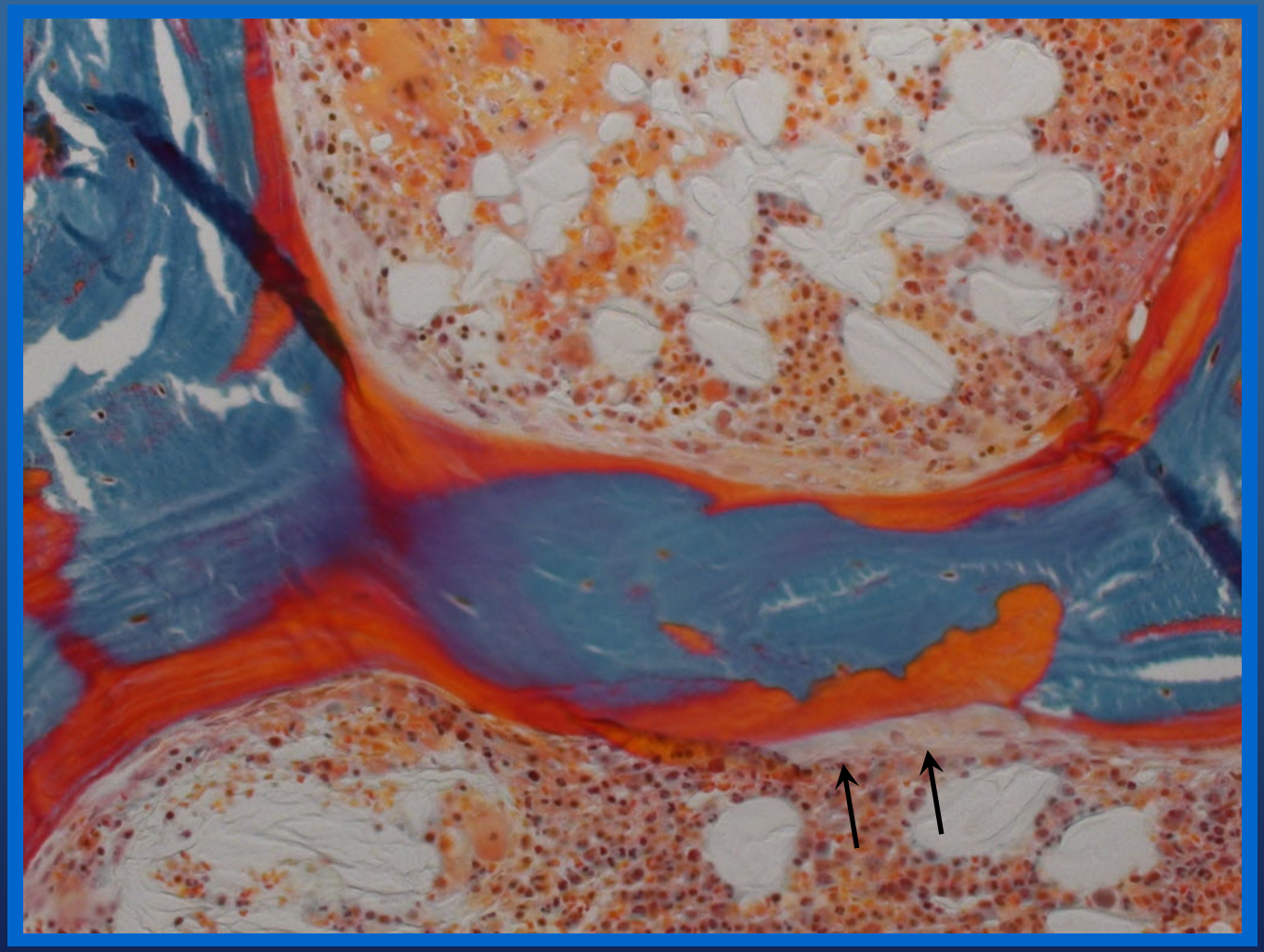






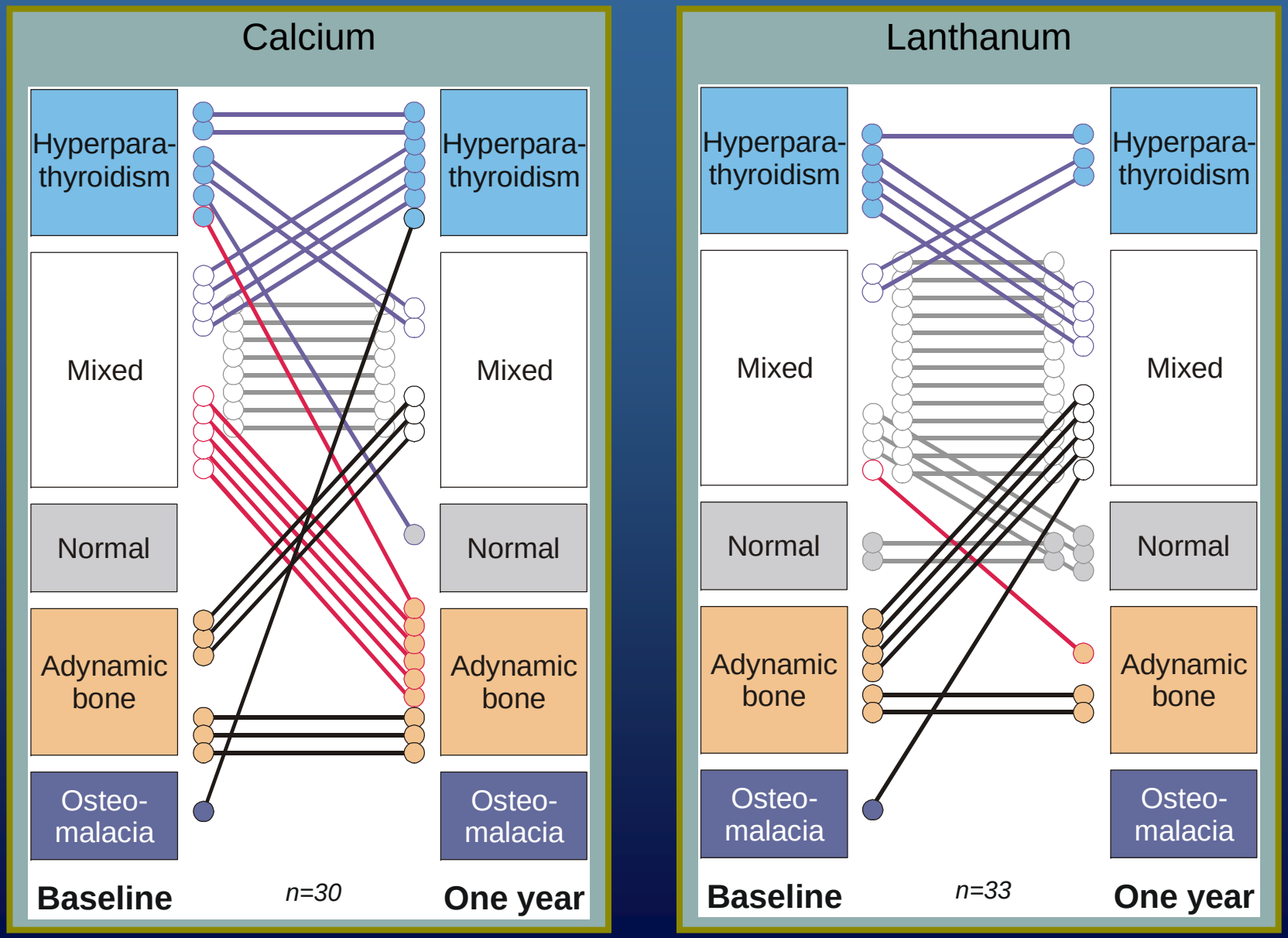


1897/2554



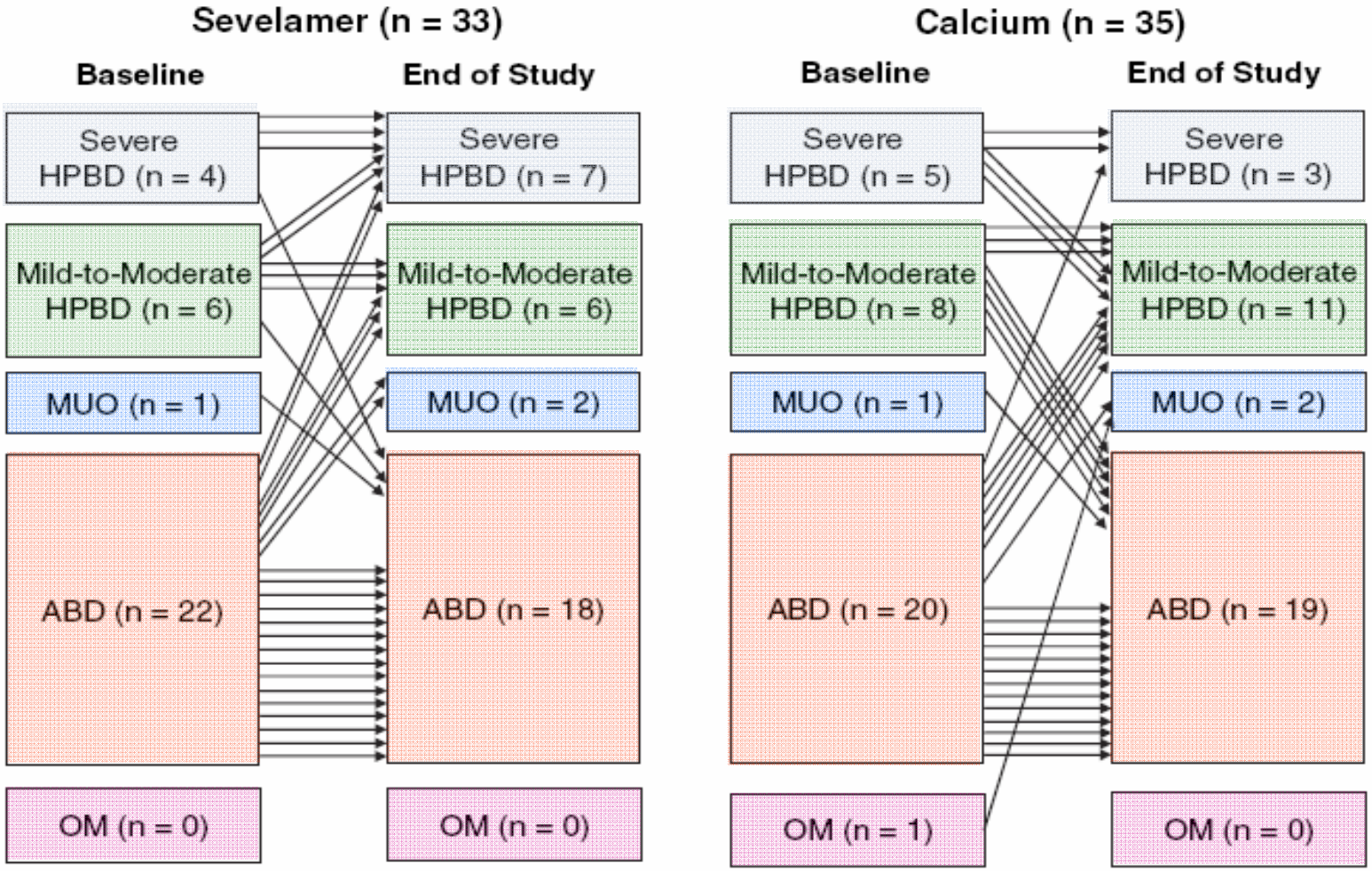
Lanthanum carbonate as a phosphate binder

One year lanthanum treatment does not induce low bone turnover



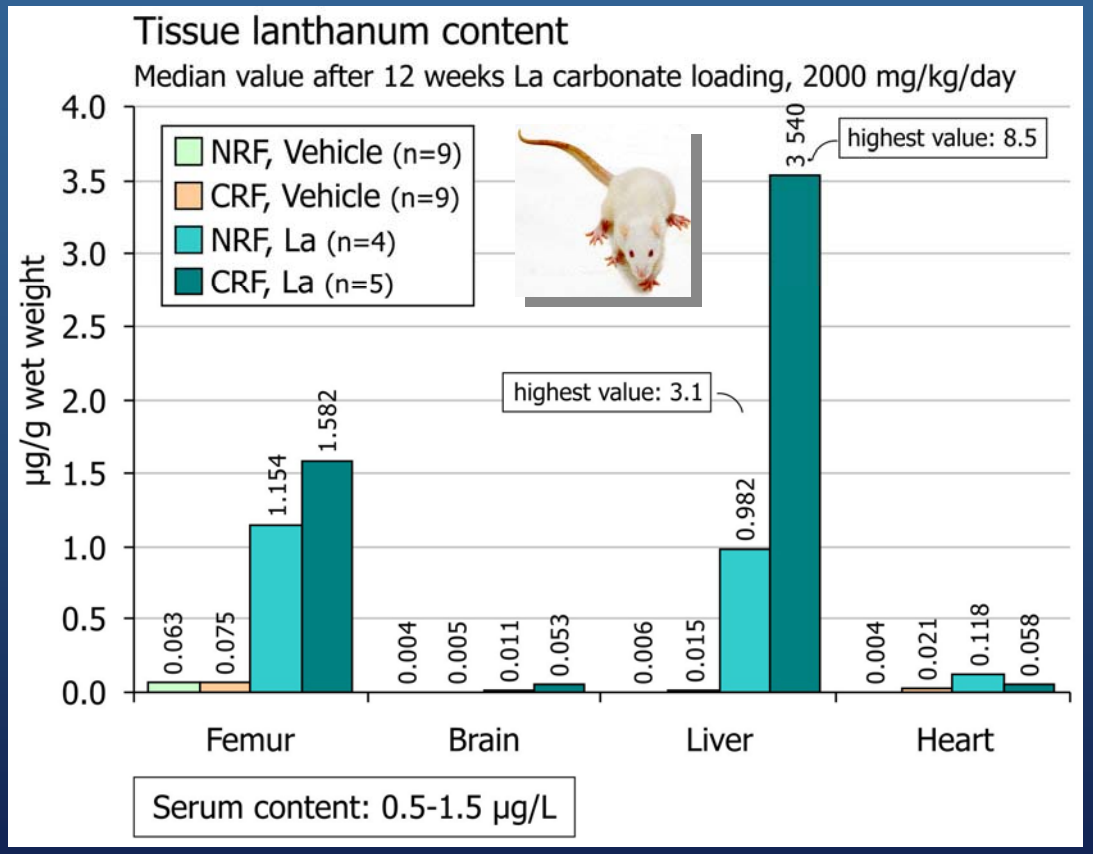
D'Haese PC et al: Kidney Int 63 (S85): 73-78, 2003 Malluche et al Clin Nephrol 70/ 285-295 /2008

Effects of sevelamer vs calcium carbonate on renal osteodystrophy



Adapted from Ferreira A et al., J Am Soc Nephrol 19: 405-412, 2008

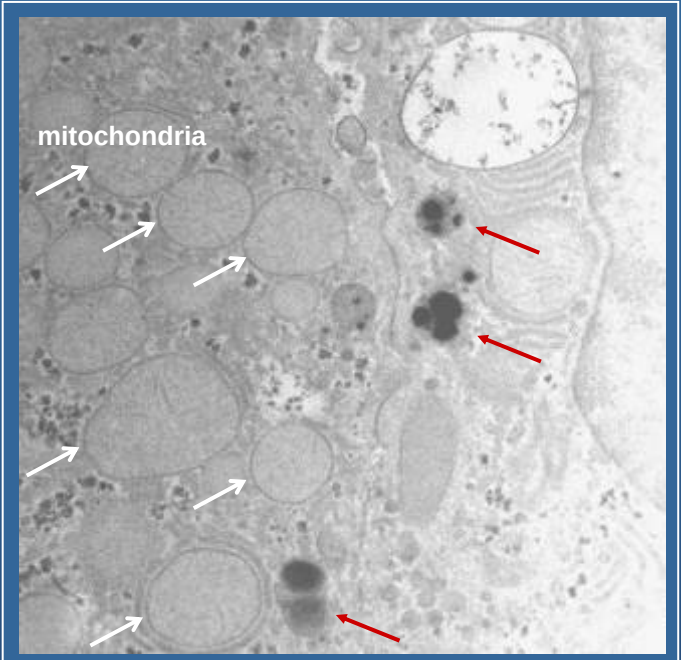
Tissue deposition of lanthanum

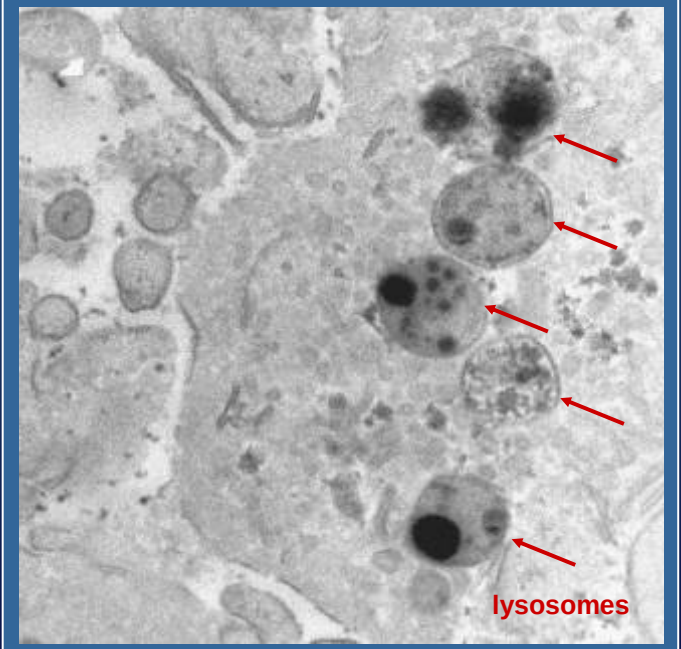


Behets G et al

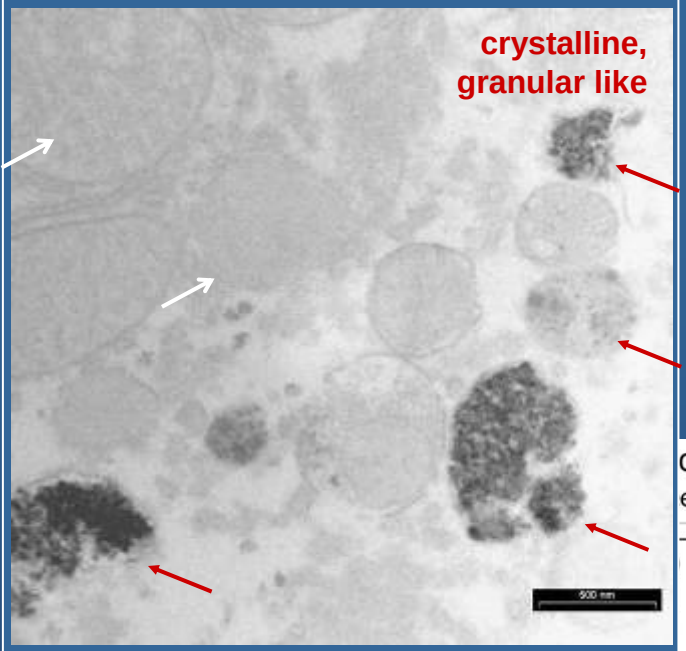
Transcellular transport of lanthanum in liver

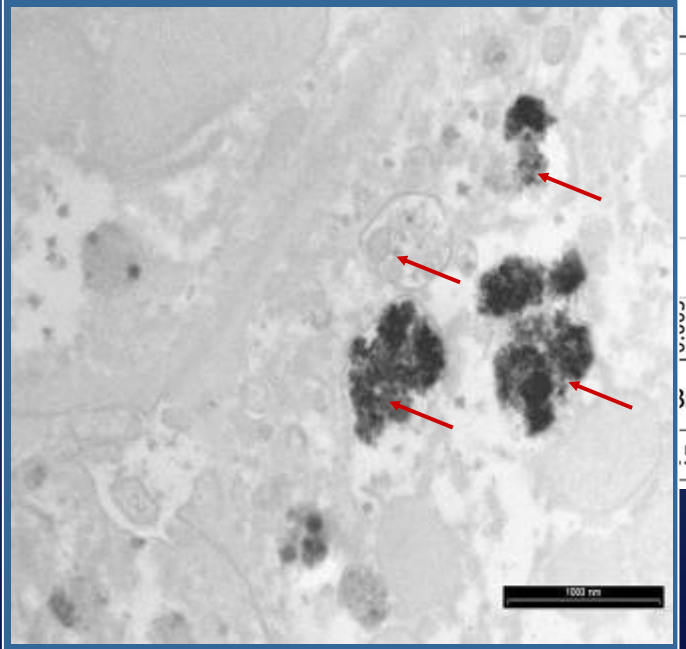
Transmission electron microscopy of liver tissue



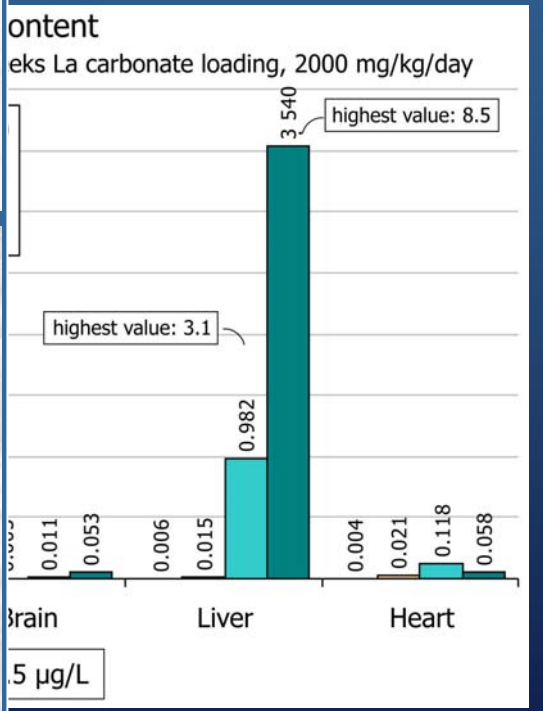


rats not exposed to lanthanum





lanthanum loaded rats
(dose: 0.3 mg/kg/day IV, 4 weeks)



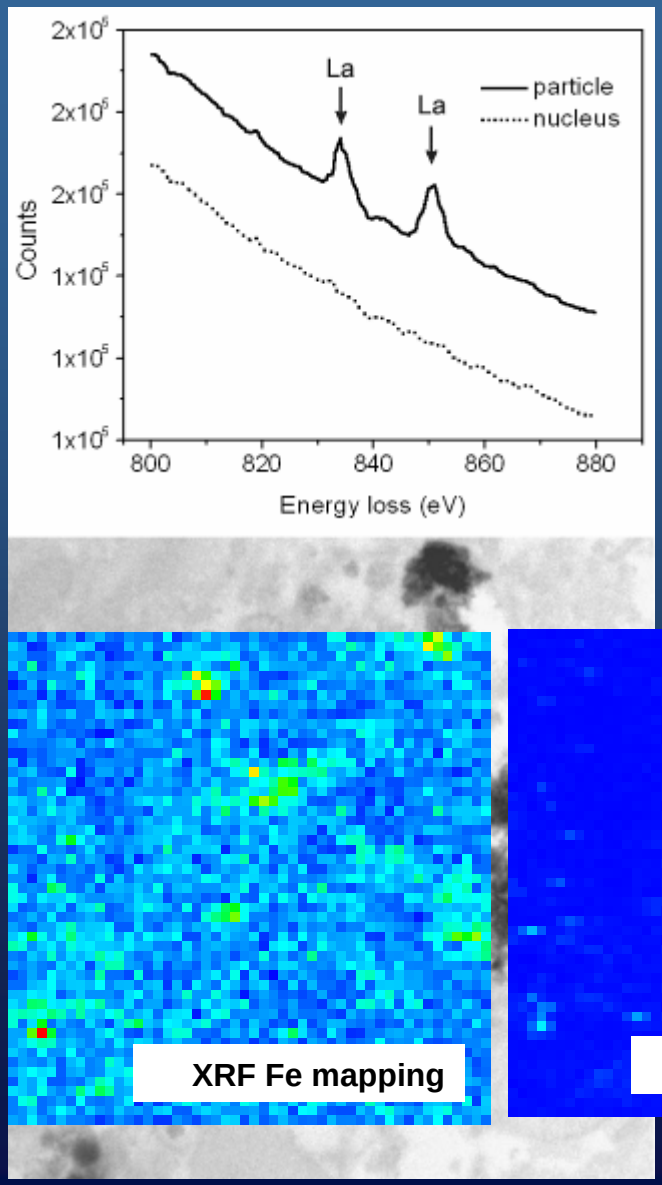
Yang Z et al:
J Microscopy
223: 133-139, 2006

F. Roels

Electron Energy Loss Spectroscopy (EELS) of liver tissue of lanthanum loaded rats

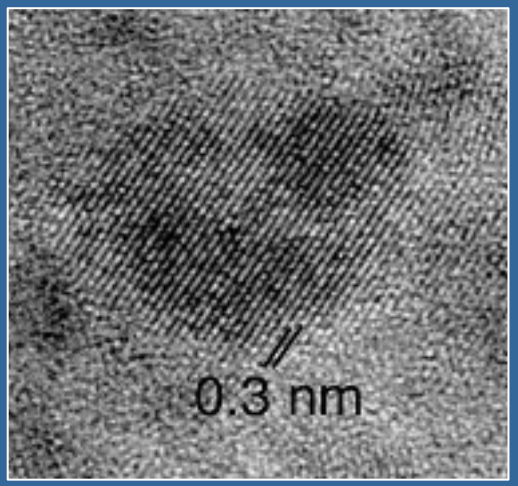
(dose: 0.3 mg/kg/day IV, 4 weeks)

Tissue deposition of lanthanum in the liver



Example of a HRTEM image of a nanoparticle in a granular lysosome

HRTEM=high resolution transmission electron microscopy



Crystallographic nature

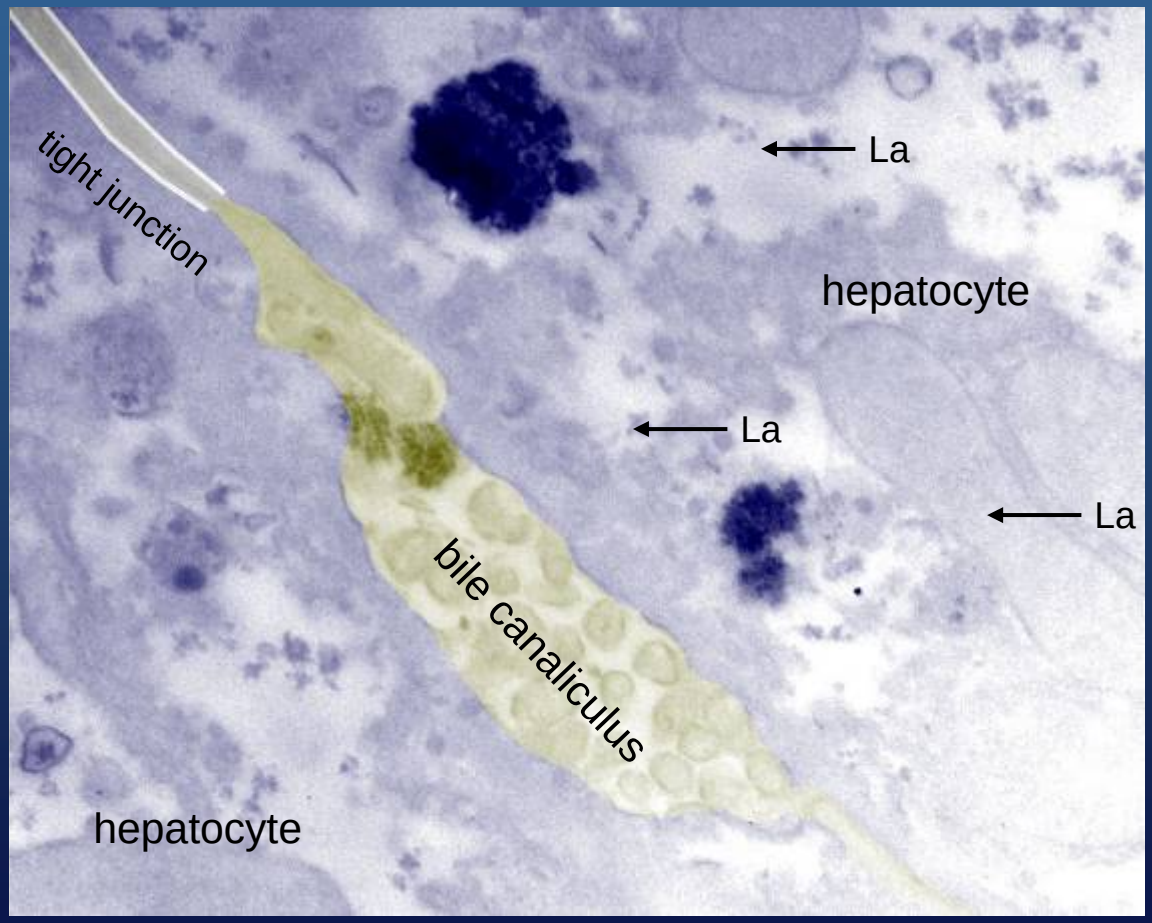
Interplanar spacing of 0.30 ± 0.02
Lanthanum phosphate structure (LaPO4)
Lattice resolution

Bervoets A. et al:
Kidney Int (in press 2008)

F. Roels

Transcellular transport of lanthanum in liver

Transmission electron microscopy of liver tissue of lanthanum loaded rats (dose: 0.3 mg/kg/day IV, 4 weeks))



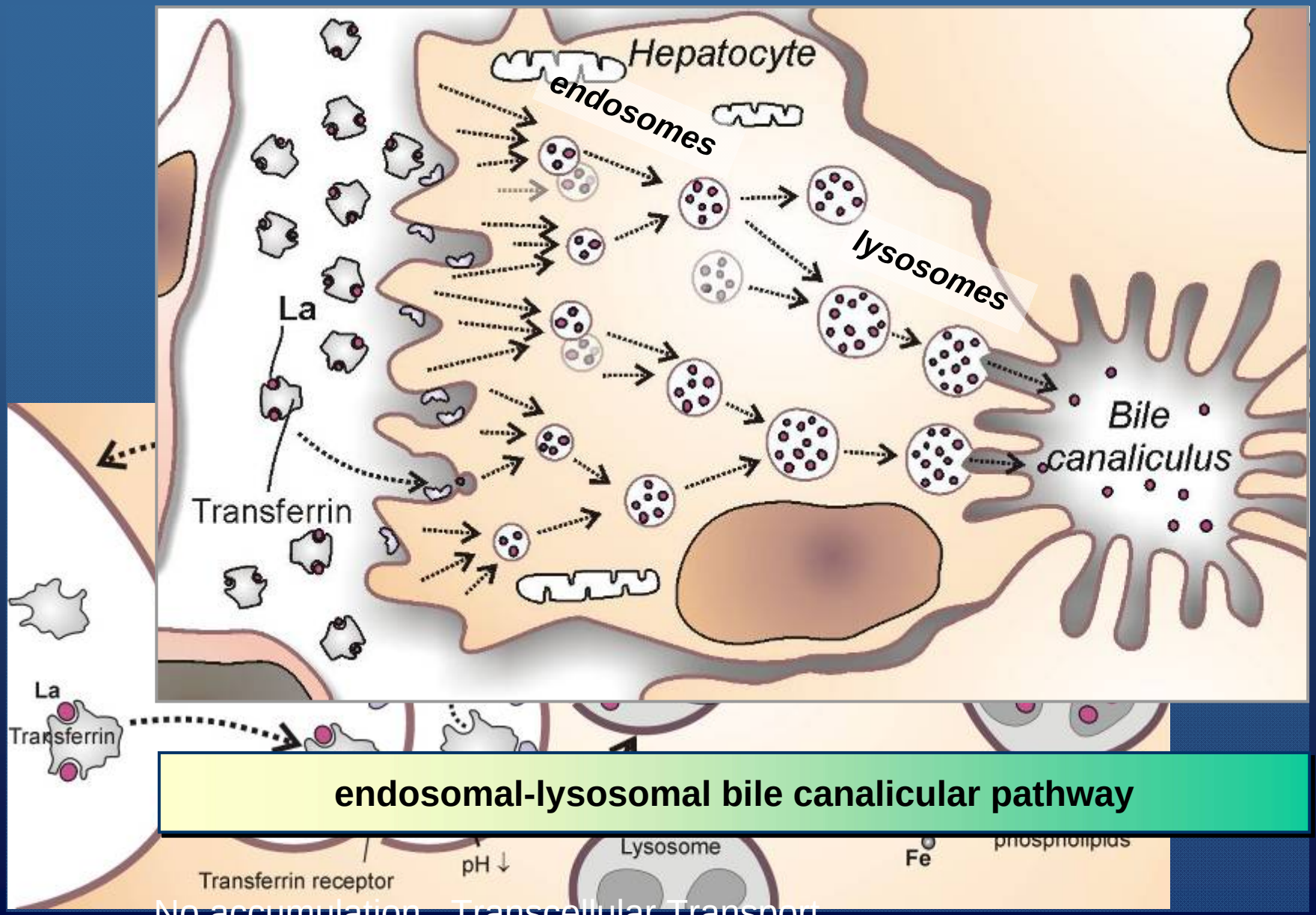
Bervoets A. et al:
Kidney Int (jan 2009)

F. Roels

Transcellular transport of lanthanum in liver

Lanthanum uptake in hepatocyte

Bervoets A. et al:
Kidney Int (in press 2008)

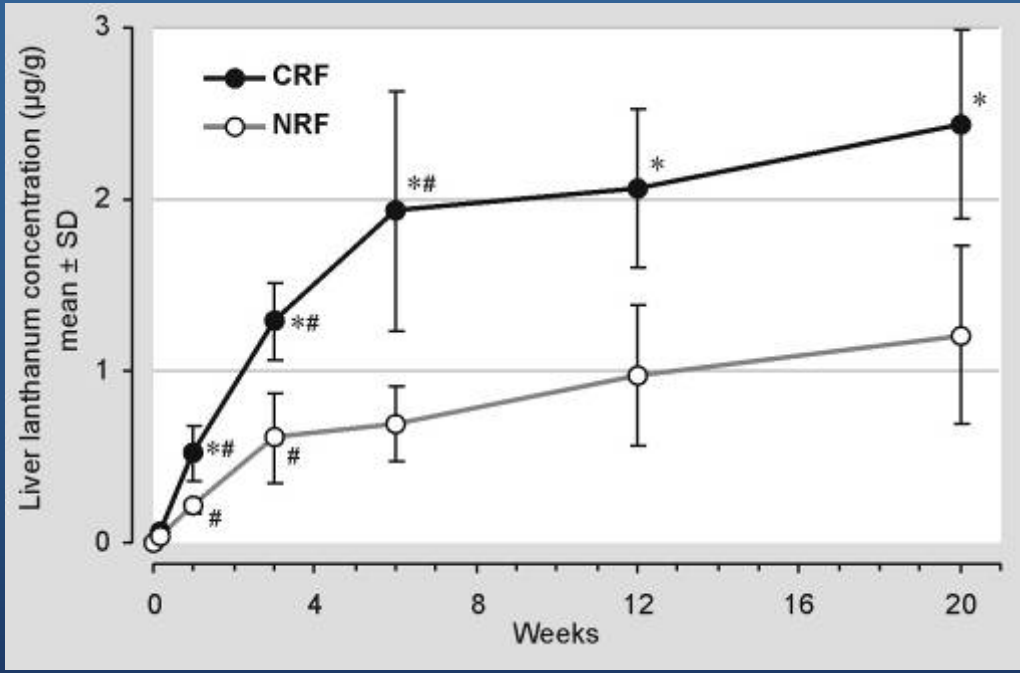


endosomal-lysosomal bile canalicular pathway

No accumulation → Transcellular Transport

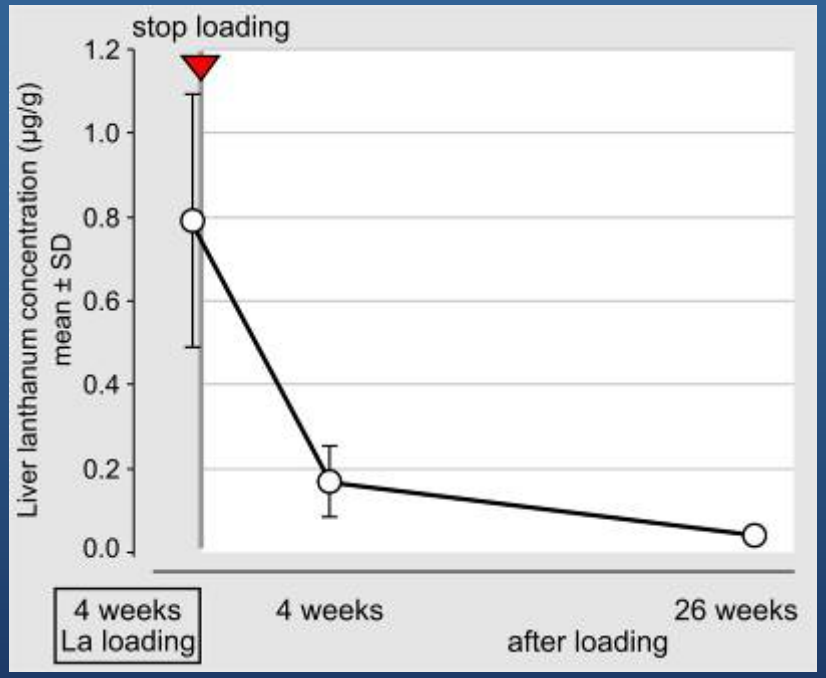
Liver handling of lanthanum

loading



Study LAN 05
Wistar rats
Males
Number/time point = 6
Dose = 1000mg/kg/day $La_2(C03)_3$
Route = oral gavage
Treatment period = 20 weeks
Samples = 1 day, 1, 3, 6, 12, 26 weeks loading
Values = mean ± SD; n=6

unloading



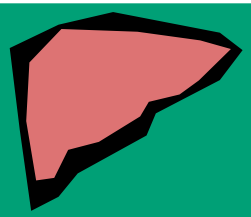
Study SPD0099
Spraque-Dawley rats
Pooled sexes (male + female)
Number/time point = 12
Dose = 1500mg/kg/day $La_2(C03)_3$
Route = oral gavage
Treatment period = 4 weeks
Samples = 4, 26 weeks after cessation of dosing
Values = mean ± SD; n=12

*: $p<0.05$ vs. NRF
#: $p<0.05$ vs. previous time point

Bervoets A. et al: Kidney Int (jan 2009)

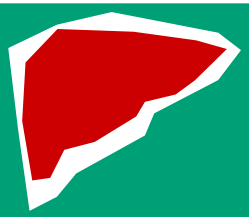
Liver concentrations of some lysosomally-stored metals (nmol/g)

La



Rat
3% La diet 110d

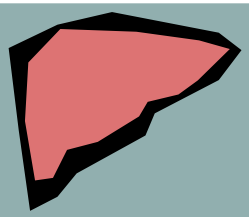
9-20 nmol/g



Human
dialysis

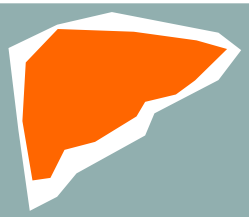
4-12 nmol/g

Fe



Rat
background:

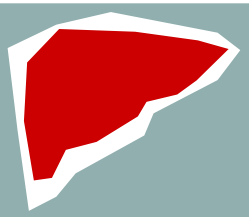
2700 ± 200
(Park, 1987)



Human
background:

1400 ± 700*
(Basset, 1996)

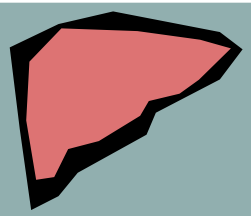
32000
(Nuttal, 2003)



Human
alcohol liver dis.:

25000 ± 25000*
(Basset, 1996)

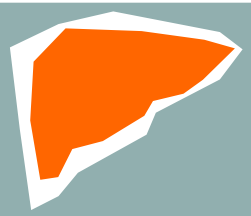
Cu



Rat
background:

279 ± 55*
(Haywood, 1980)

280 ± 24*
(Haywood, 1985)

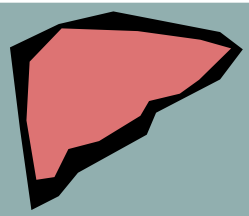


Human
background:

300 – 800*
(Brewer, 1988)

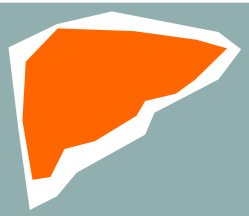
860
(Nuttal, 2003)

Al



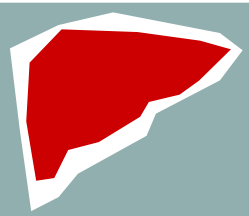
Rat
background:

15
(Berlyne, 1972)



Human
background:

150 ± 60
(Alfrey, 1980)

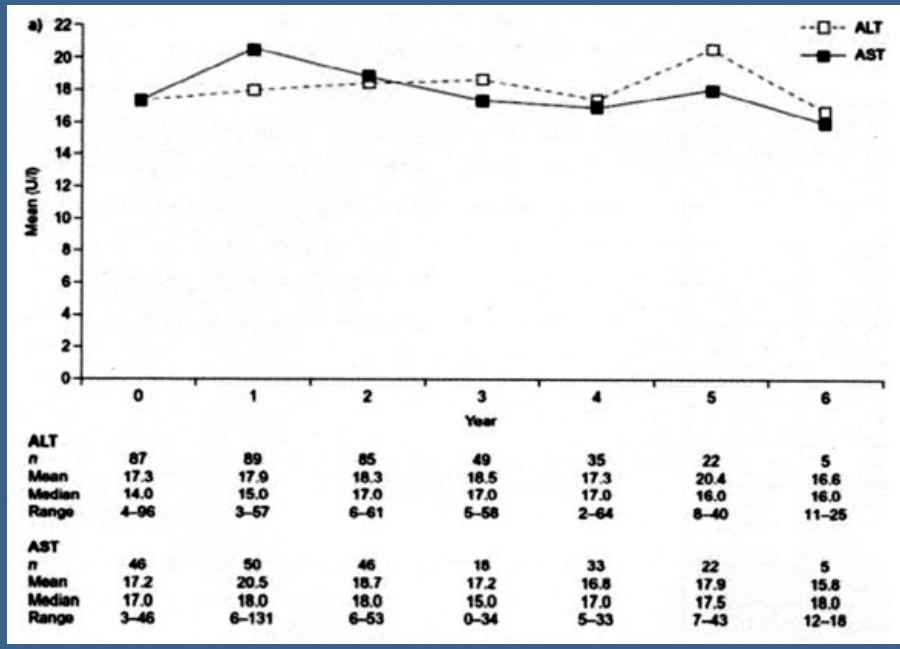


Human
dialysis
encephalopathy:

11000 ± 800
(Alfrey, 1980)

*** Dry weight (otherwise all values are wet weight)**

Lanthanum carbonate treatment, for up to 6 years, is not associated with adverse effects on the liver in patients with chronic kidney disease stage 5 receiving hemodialysis

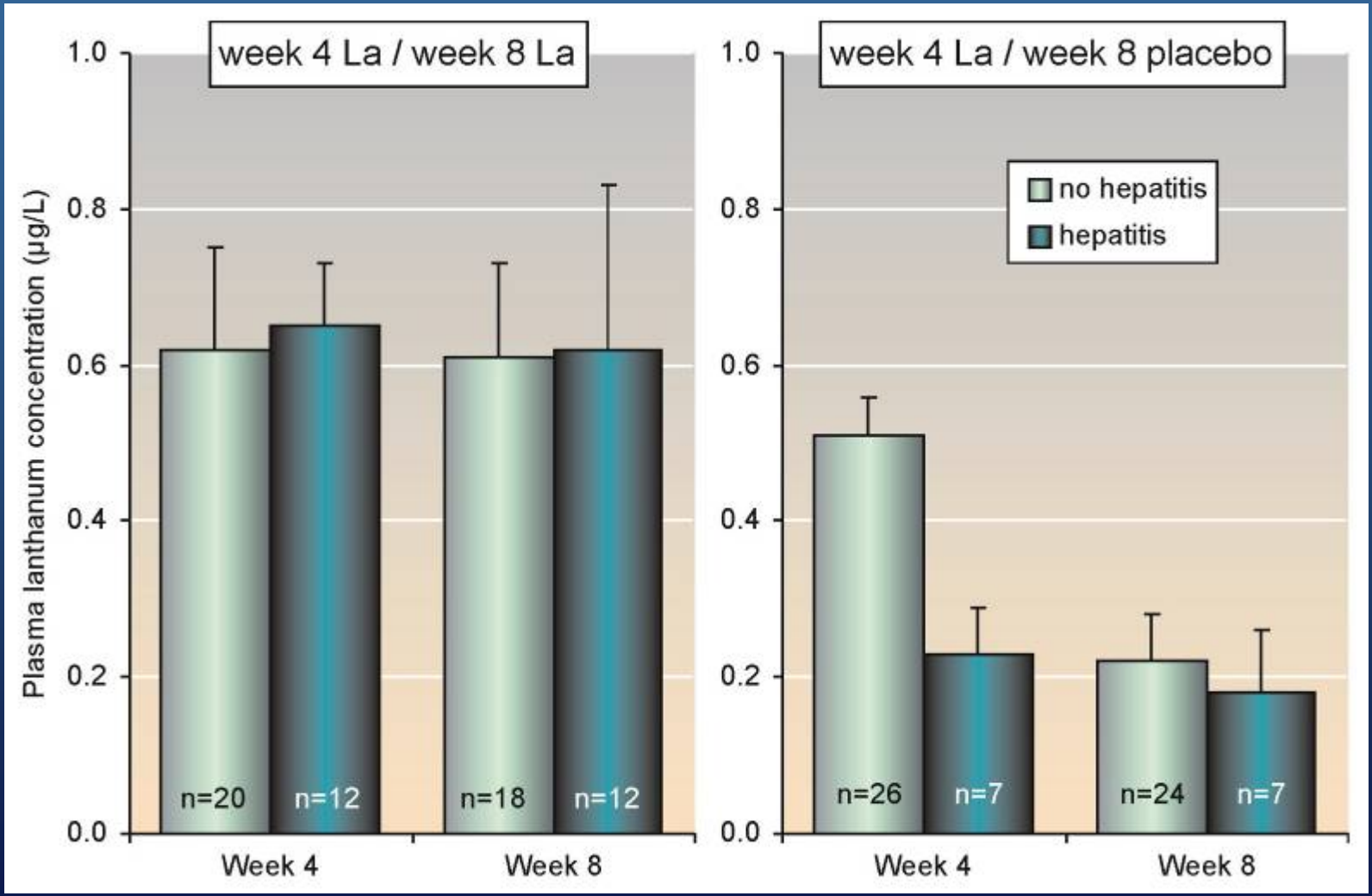


	0	1	2	3	4	5	6
ALT							
n	87	89	85	49	35	22	5
Mean	17.3	17.9	18.3	18.5	17.3	20.4	16.6
Median	14.0	15.0	17.0	17.0	17.0	16.0	16.0
Range	4–96	3–57	6–61	5–58	2–64	8–40	11–25
AST							
n	46	50	46	18	33	22	5
Mean	17.2	20.5	18.7	17.2	16.8	17.9	15.8
Median	17.0	18.0	18.0	15.0	17.0	17.5	18.0
Range	3–46	6–131	6–53	0–34	5–33	7–43	12–18

	0	1	2	3	4	5	6
n	88	89	84	49	35	22	5
Mean	0.38	0.39	0.40	0.46	0.35	0.28	0.26
Median	0.35	0.40	0.39	0.44	0.30	0.20	0.20
Range	0.20–0.77	0.20–0.80	0.20–0.81	0.20–1.03	0.20–1.00	0.20–0.50	0.20–0.50

Hutchison AJ et al: Clin Nephrol 71: 286-295, 2009

Study 315: Plasma La Levels: effect of hepatitis



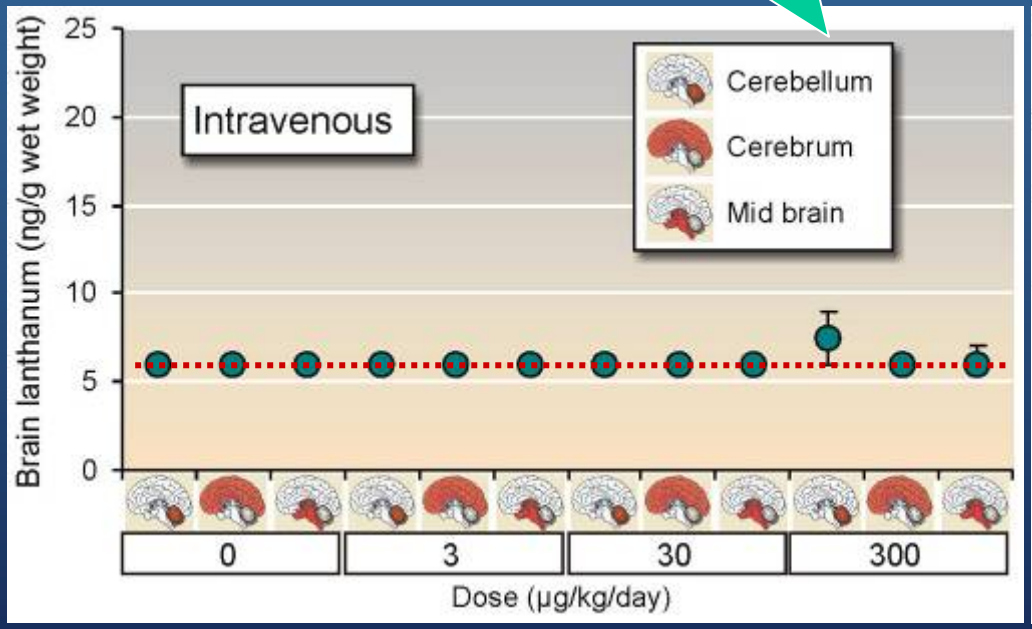
No Hep+ patients had elevated bilirubin levels and Hepatic enzymes were similar in both groups

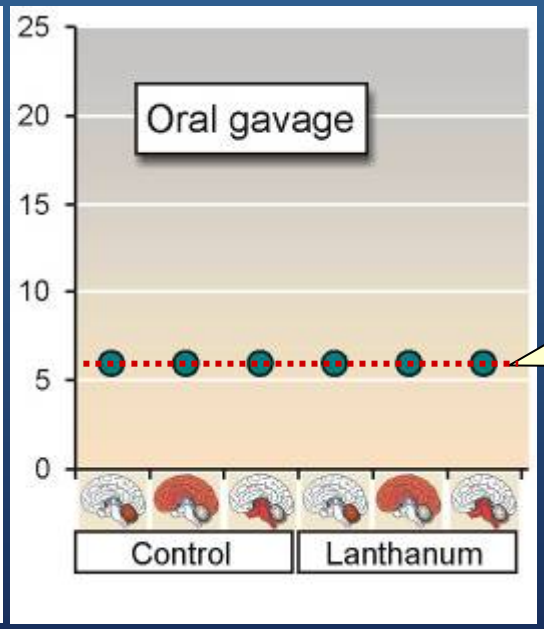
Absence of deposition of lanthanum in brain

Unquantifiable brain lanthanum levels in rats with normal renal function

Plasma lanthanum concentration 1560 ng/mL (>1500 times human Cmax)

Sacchiero et al (2003)
JASN; 14; 205A; ABSTRACT
Lanthanum concentrations 2499 ± 3754 ng/g
Genzyme-sponsored study





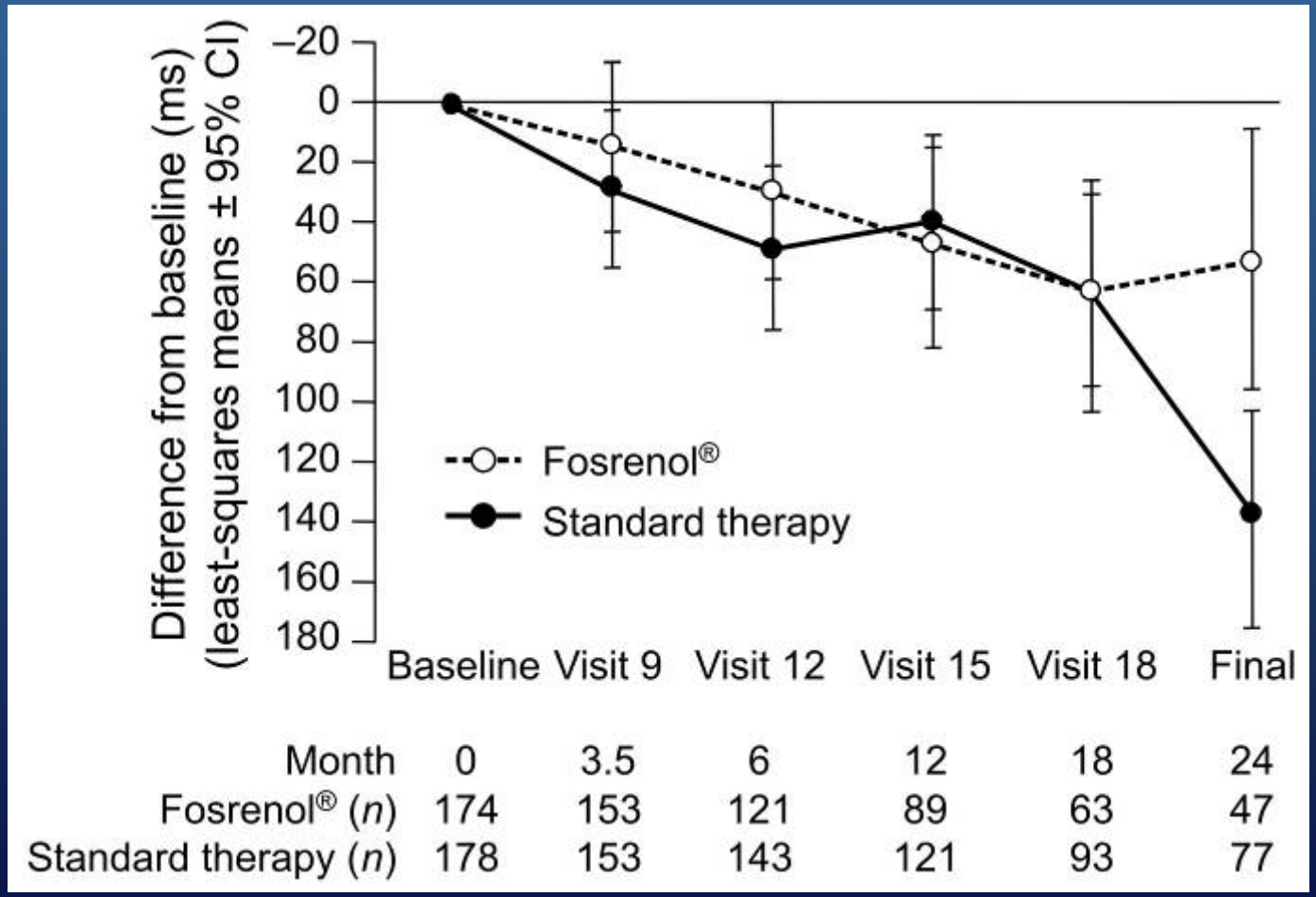
Rat NRF
Intravenous bolus
Treatment period : 4 weeks
Dose : 3, 30 or 300 µg/kg/day
N=12, Median, 25th & 75th %

Rat NRF
Oral gavage
Treatment period : 4 weeks
Dose : 1500 mg/kg/day
N=12, Median, 25th & 75th %

Shire Studies : SPD0099, SPD0102

Cognitive deterioration not accelerated

- **Deterioration in cognitive function scores similar in patients treated with Fosrenol® or standard therapy**



Month	0	3.5	6	12	18	24
Fosrenol® (*n*)	174	153	121	89	63	47
Standard therapy (*n*)	178	153	143	121	93	77

A

Altmann P *et al*., *Kidney International*; in press

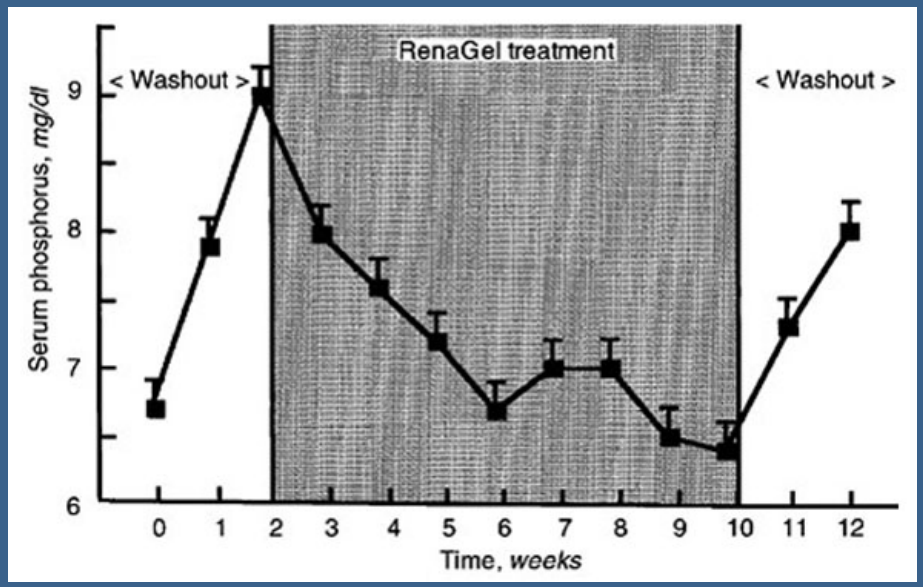
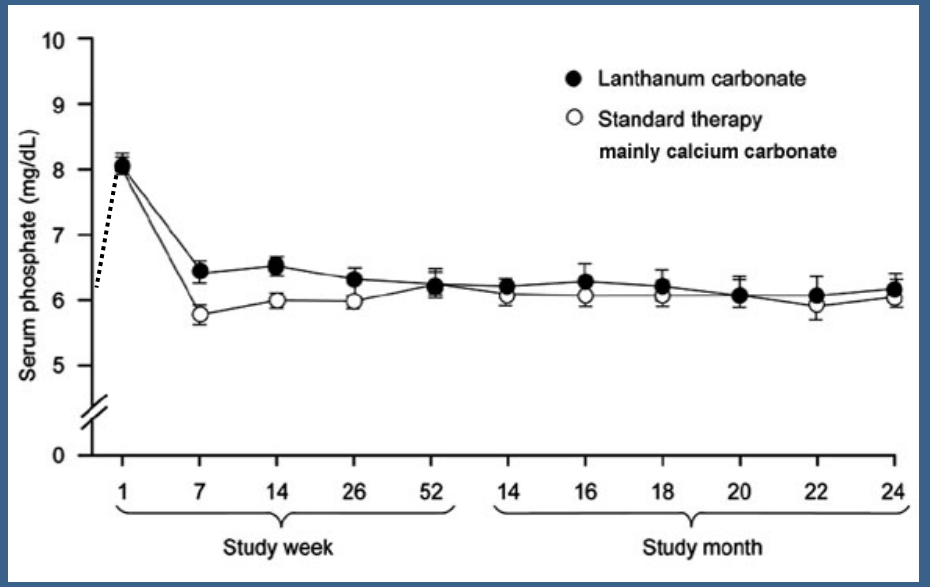
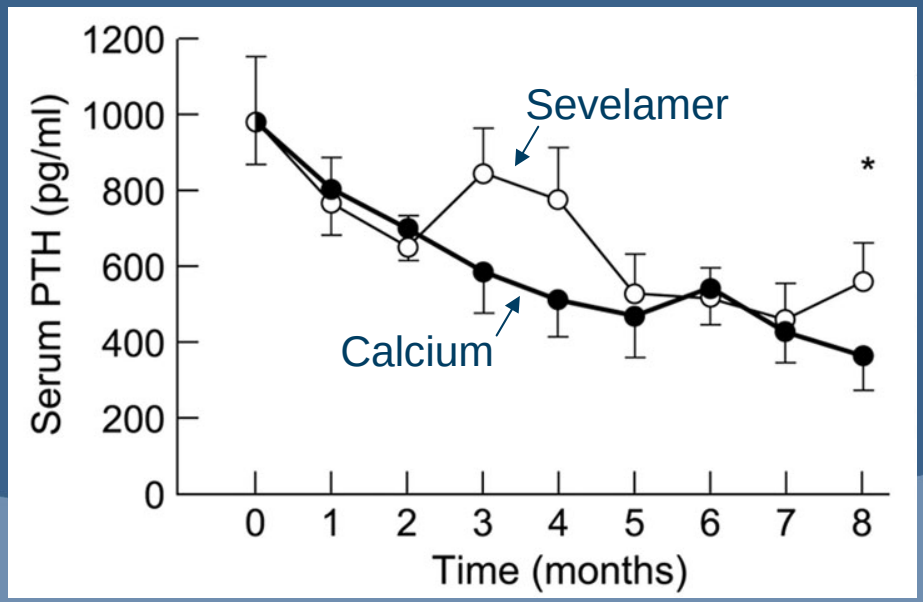
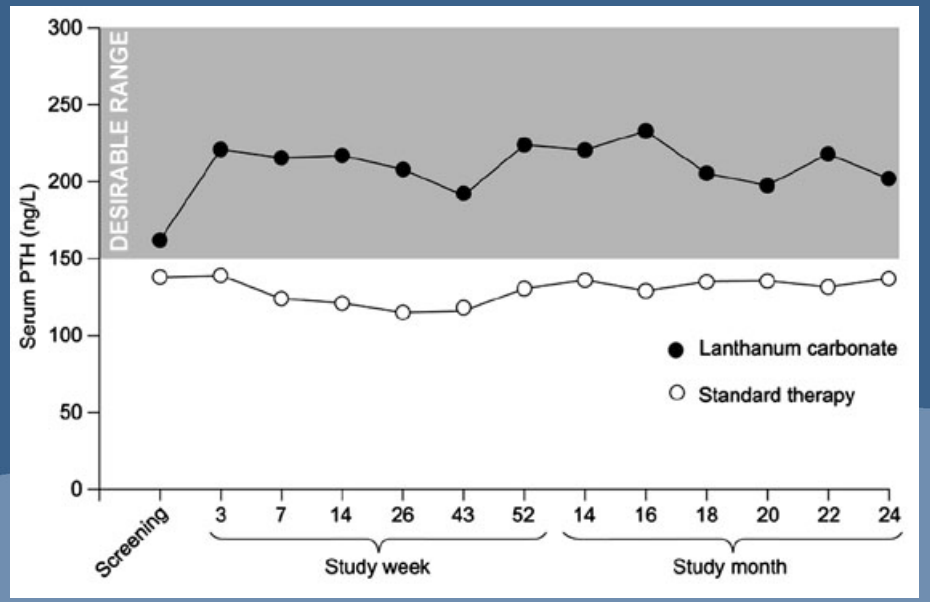
Kidney Bone Disease
What happens when the kidney fails?

- ✓ Progression of kidney damage >> mineral metabolism
- ✓ Bone histology in ESRF
- ✓ Concept of calcium loading in CKD
- ✓ Non-calcium containing phosphate binders
- ✓ Lanthanum: a safe phosphate binder?
- ➢ Lanthanum and the calcium loading concept

M.E. De Broe
Stockholm
31 March 2009

Universiteit Antwerpen

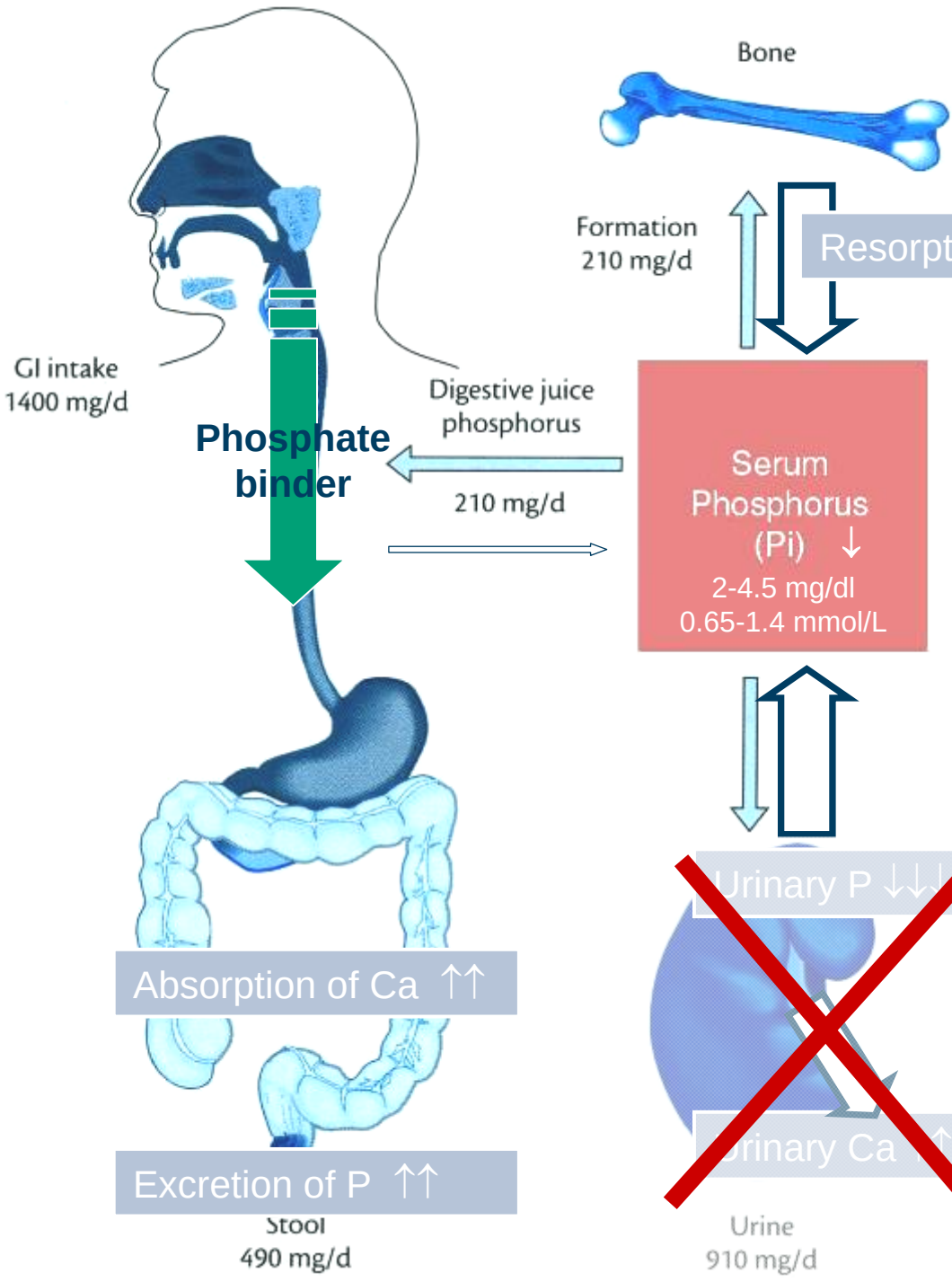
Non calcium containing phosphate binders

	Renagel (n= 172)	**Lanthanum** (n= 682 La, n=677 controls)
Serum P		
Serum PTH		

Slatopolsky EA et al: Kidney Int 55: 299-307, 1999

Finn WF et al: Clin Nephrol 65: 191-202, 2006

Effect of phosphate binder



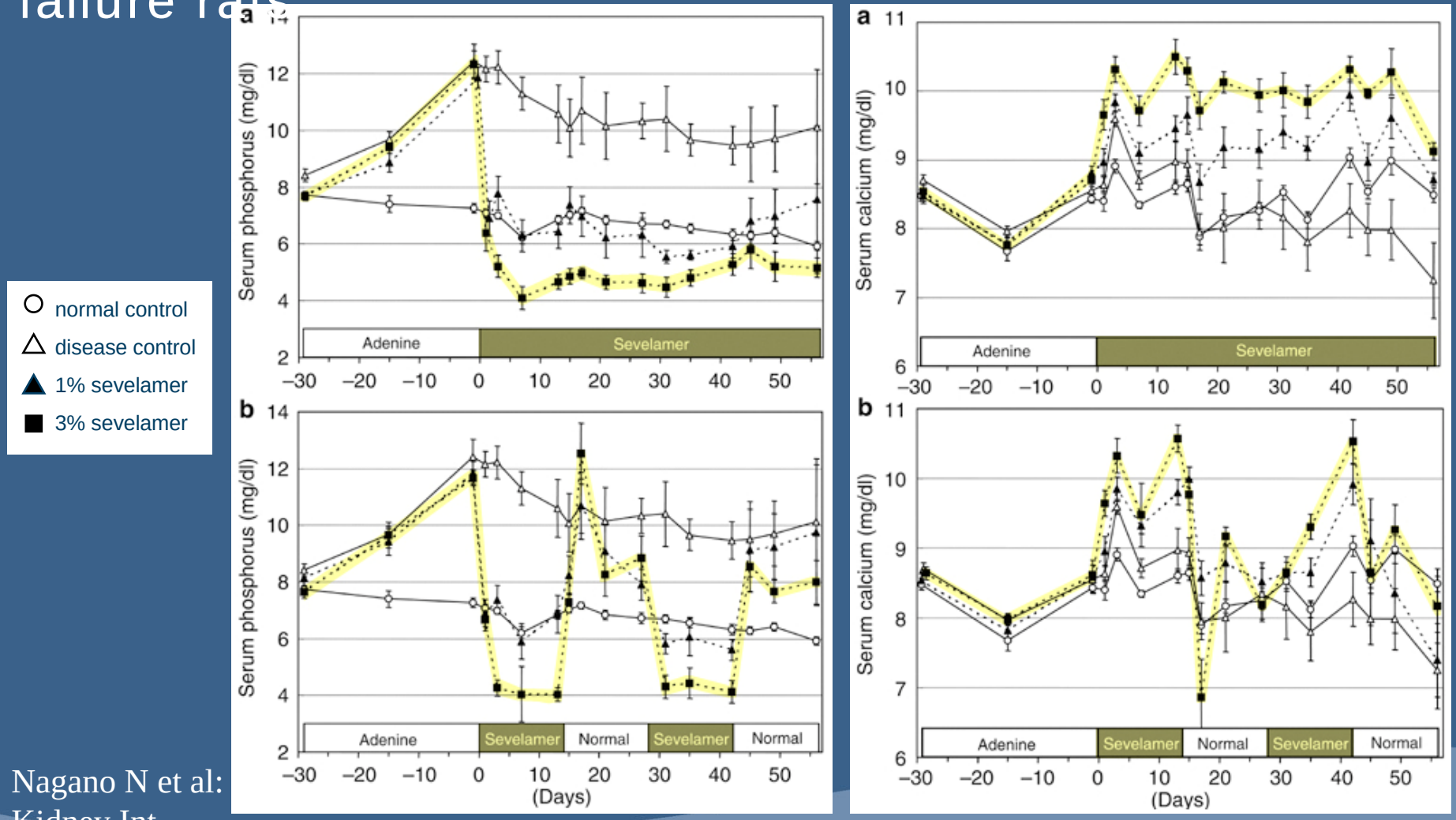
- Ø Bone Demineralization
- Ø Osteomalacia

Foldes J et al: Bone 12: 67-71, 1991

DIALYSIS PATIENT

Evidence for a phosphorus-depletion syndrome in man.
New Engl J Med 278: 409-415, 1968

Effect of manipulating serum phosphorus with phosphate binder on circulating PTH and FGF23 in renal failure rats

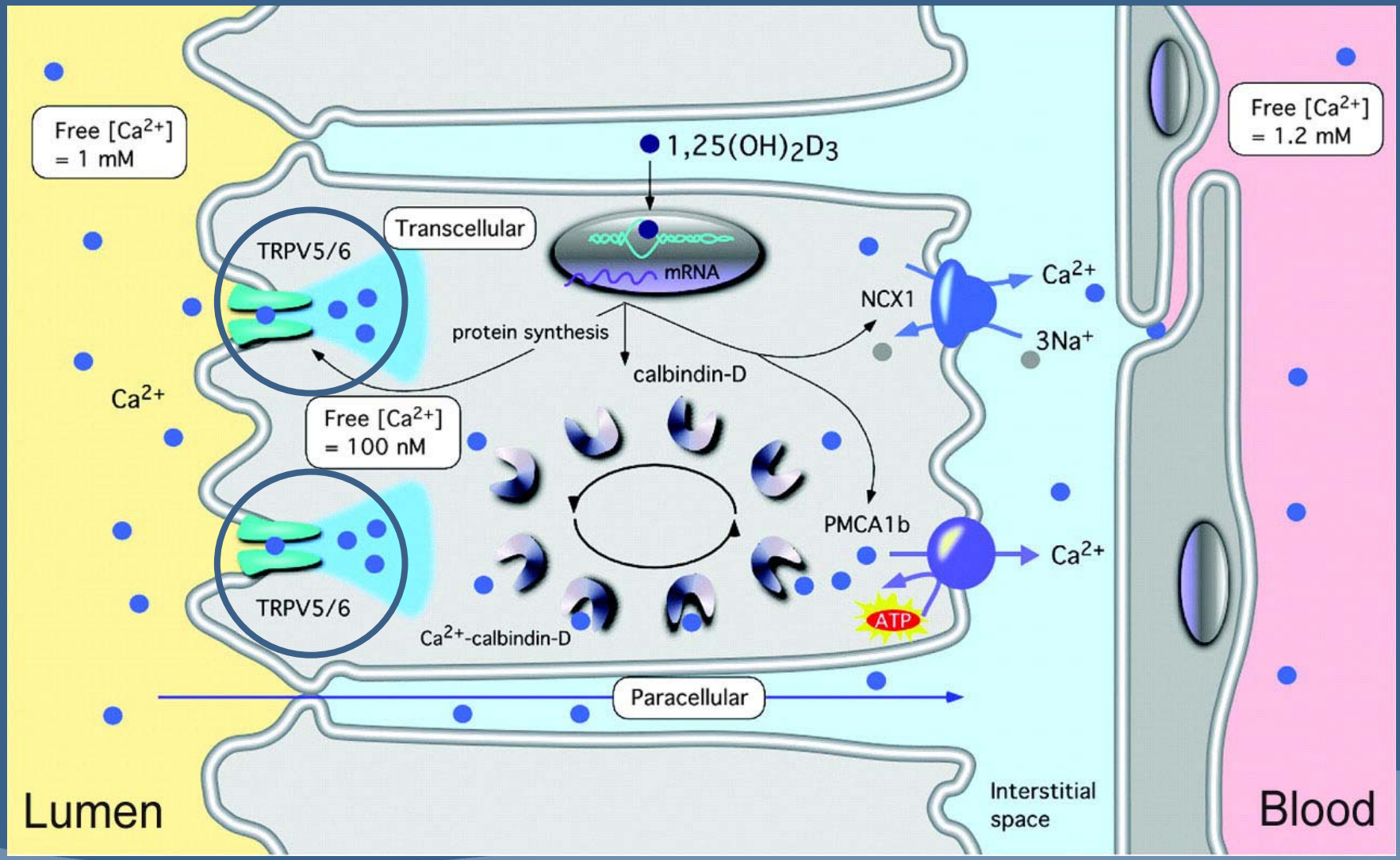


Nagano N et al: Kidney Int 69: 531-537, 2006

Effects of (a) continuous and (b) intermittent treatment with sevelamer on serum phosphorus (left) and calcium (right) levels

Mechanism of epithelial Ca^{2+} transport ,

Calcium absorption across epithelia



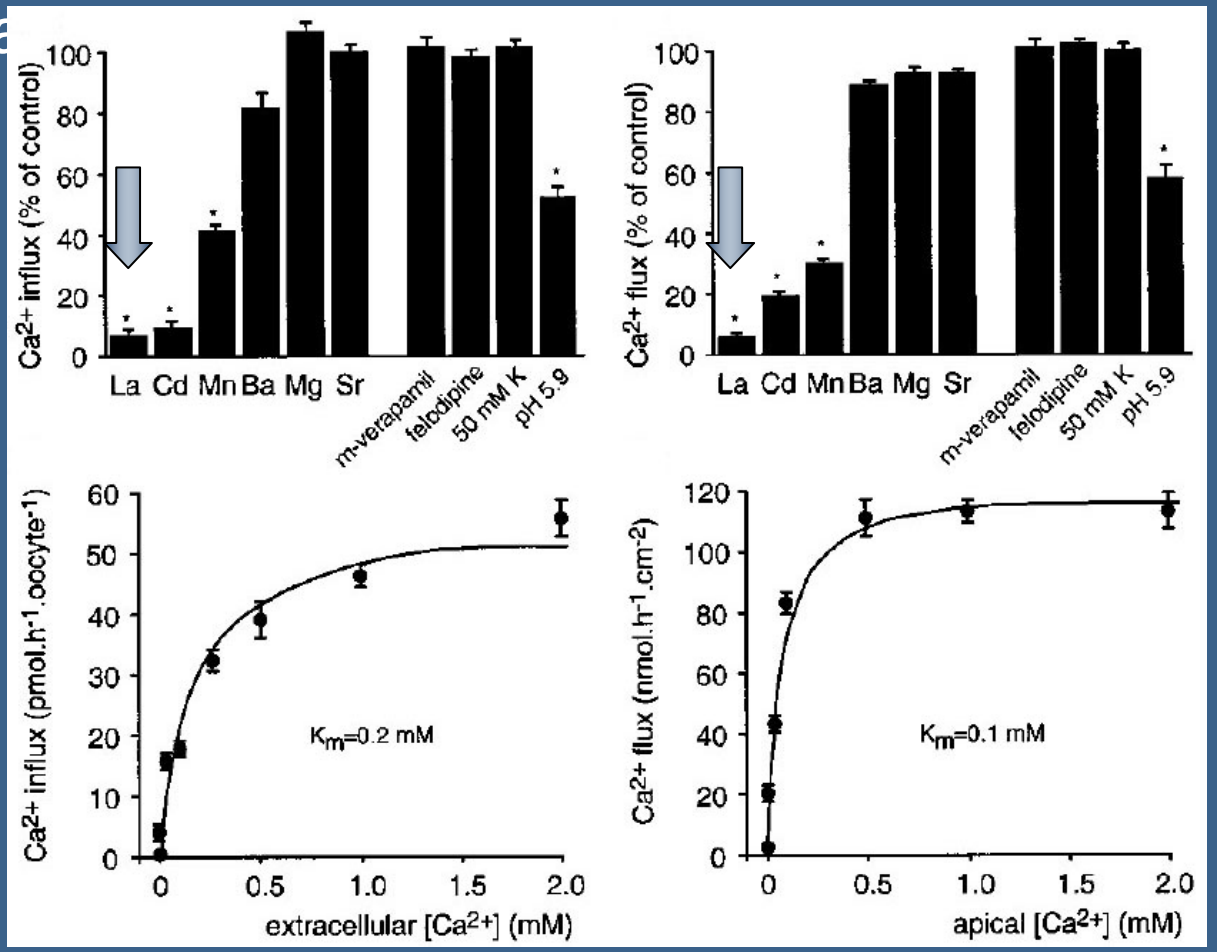
Hoenderop JG et al: Physiol Rev 85: 373-422, 2005

Calcium sensing receptor

Molecular identification of the apical Ca^{2+} channel in 1,25-dihydroxyvita

Hoenderop JG et al: J Biol Chem 274: 8375–8378, 1999

Functional characterization of the epithelial Ca^{2+} channel



La dose: 0.5 mM

Serum La = 3-15 nM

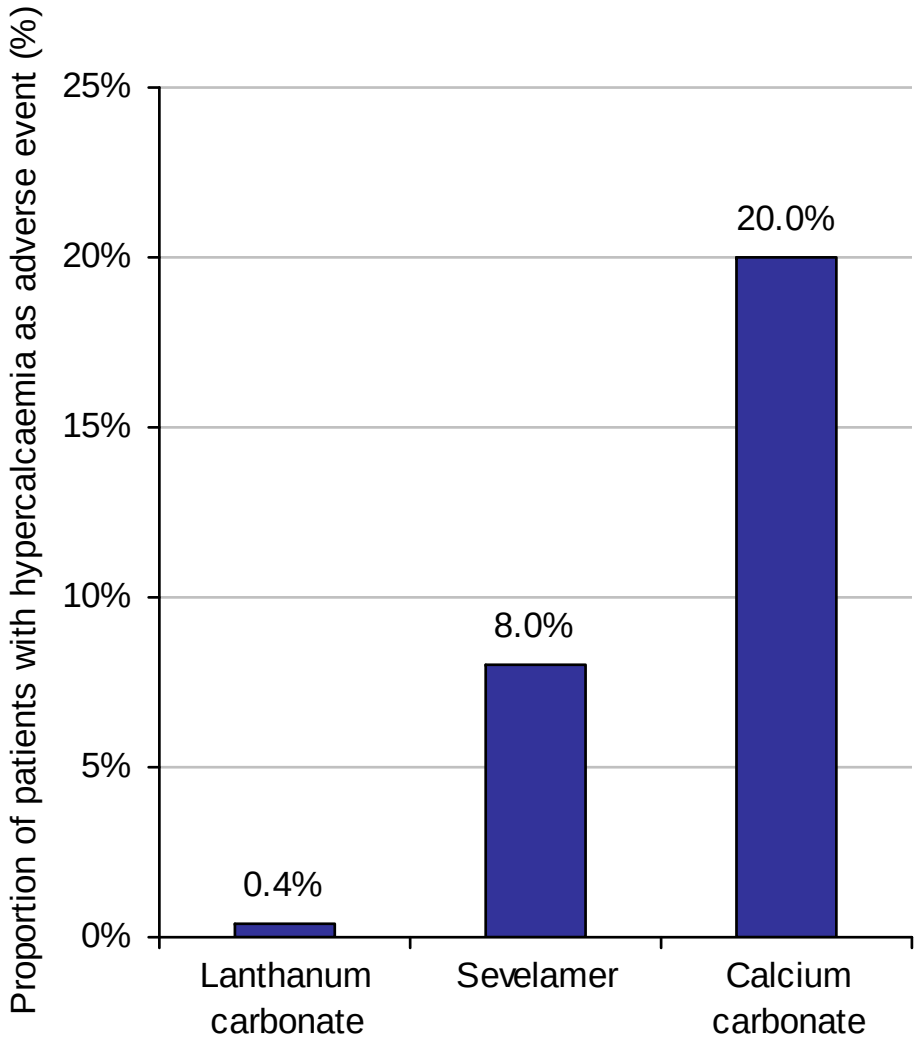
Fosrenol® (La carbonate) treatment: 2.5 – 4 g/day oral

La > 99% bound to serum proteins

Free La < 0.03-0.15 nM

NO Calcium Channel Blocking Effect

Incidence of hypercalcaemia based on a recent literature survey



Shire Pharmaceutical Contracts Ltd. Fosrenol® – Summary of Product Characteristics 2006
Hutchison A *et al. Nephron Clin Pract* 2005;100:8–19

Why do we need a choice for non - calcium phosphate binders ?

- Historical
  - Al OH_3 ✗ Toxicity (Blood, Brain & Bone)
  - Ca CO_3 ✗ Toxicity (Cardiovascular Disease)
- Current
  - Ca CO_3 ✗ Toxicity (Cardiovascular Disease)
- Newer
  - Sevelamer
  - Lanthanum

Tolerability (30% Major GI Problems)

Choice !

Why Non Calcium containing phosphate binders

Lack of toxicity

- the aluminum story
- Calcium overload calcifications

Efficacy of Lanthanum ,Sevelamer, as phosphate binders

Calcium balance La versus Sevelamer

Pill burden

People Involved

27 September 2009

University of Antwerp, Belgium

- BEHETS Geert
- BERVOETS An
- DAMS Geert
- DAUWE Simonne
- DE BEUF Annelies
- DE BROE Marc
- DE WEERDT Dirk
- D'HAESE Patrick
- GERYL Hilde
- HUFKENS Annemie
- LAMBERTS Ludwig
- MARIJNISSEN Rita
- NEVEN Ellen
- PERSY Veerle
- SPAEPEN Gie
- VERBERCKMOES Steven
- VERHULST Anja
- VERVAET Benjamin

Shire Pharmaceuticals, UK

- **DAMMENT Stephen**
- **STOKES Diana**
- **PENNICK Michael**

FWO
IWT
EC
Univ Antw.
Shire

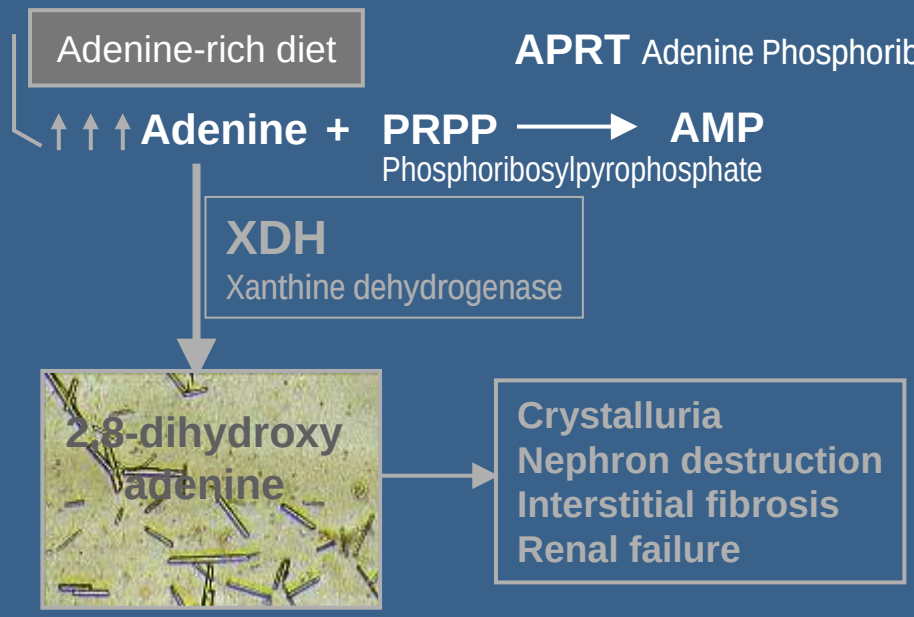
- **ROELS Frank**
  Pathology, Univ. Ghent, Belgium
- **SCHRYVERS Nick, YANG Zhiqing**
  Physics, Univ. Antwerp, Belgium
- **SUSINI J., SALOMÉ M.,**
  European Synchrotron Radiation Facility, Grenoble, France
- **DENTON J.**
  Musculoskeletal Res., Univ. Manchester, UK
- **McLEOD C., COX A.**
  Analytical Sc., Univ. Sheffield, UK
- **BLUST R., SELENS M.**
  Biology, Univ. Antwerp, Belgium

ERIK
DIRK
PATRICK

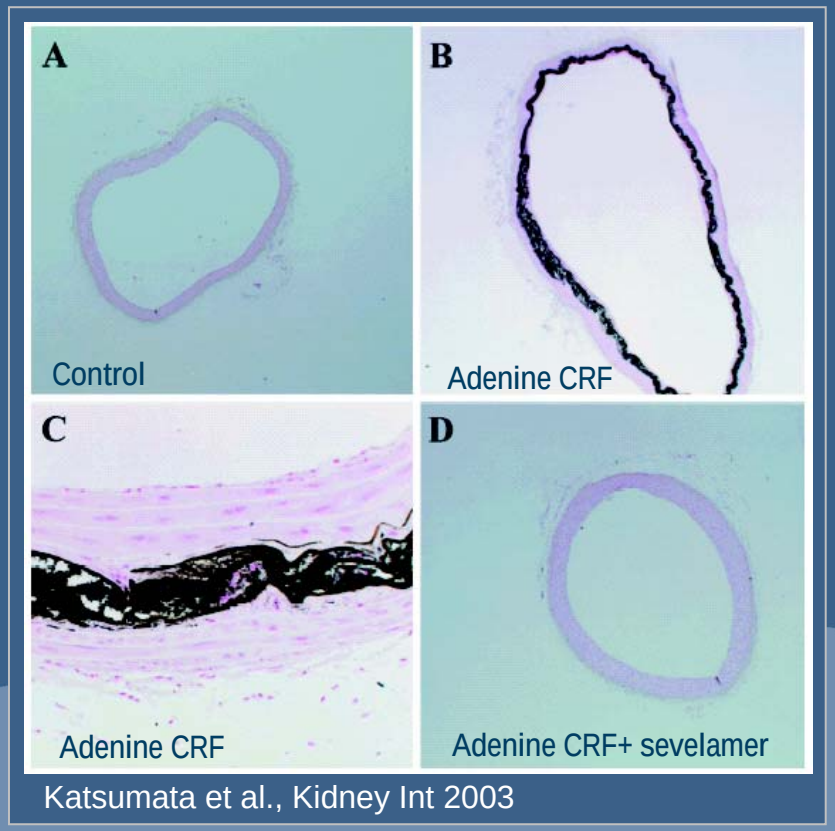
Vascular calcification

Experimental models of chronic renal failure

- Adenine-induced chronic renal failure
  - Not suitable to study renal histology
  - Reproducible, moderate CRF: serum creatinine ≈ 2.5- 3 mg/dl
  - Lipid metabolism disturbances



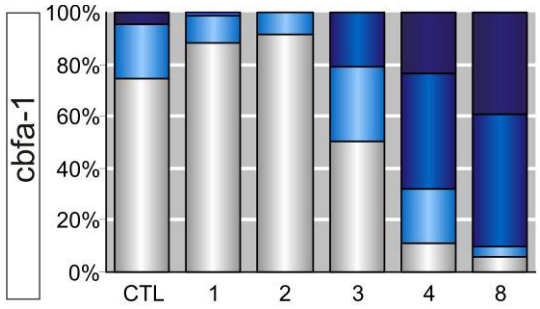
Yokozawa, Nephron 1986, Okada Clin Exp Immunol 1999

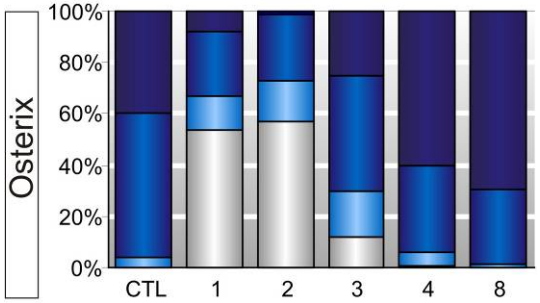


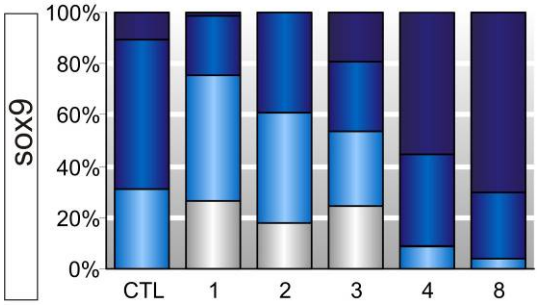
Katsumata et al., Kidney Int 2003

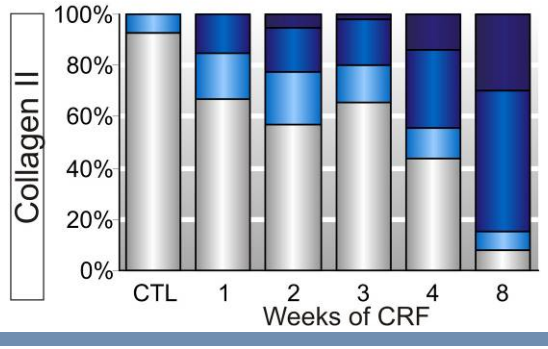
Adenine-low protein CRF rat model

Time-dependent increase of osteo-chondrocyte bone markers in association with the calcification process



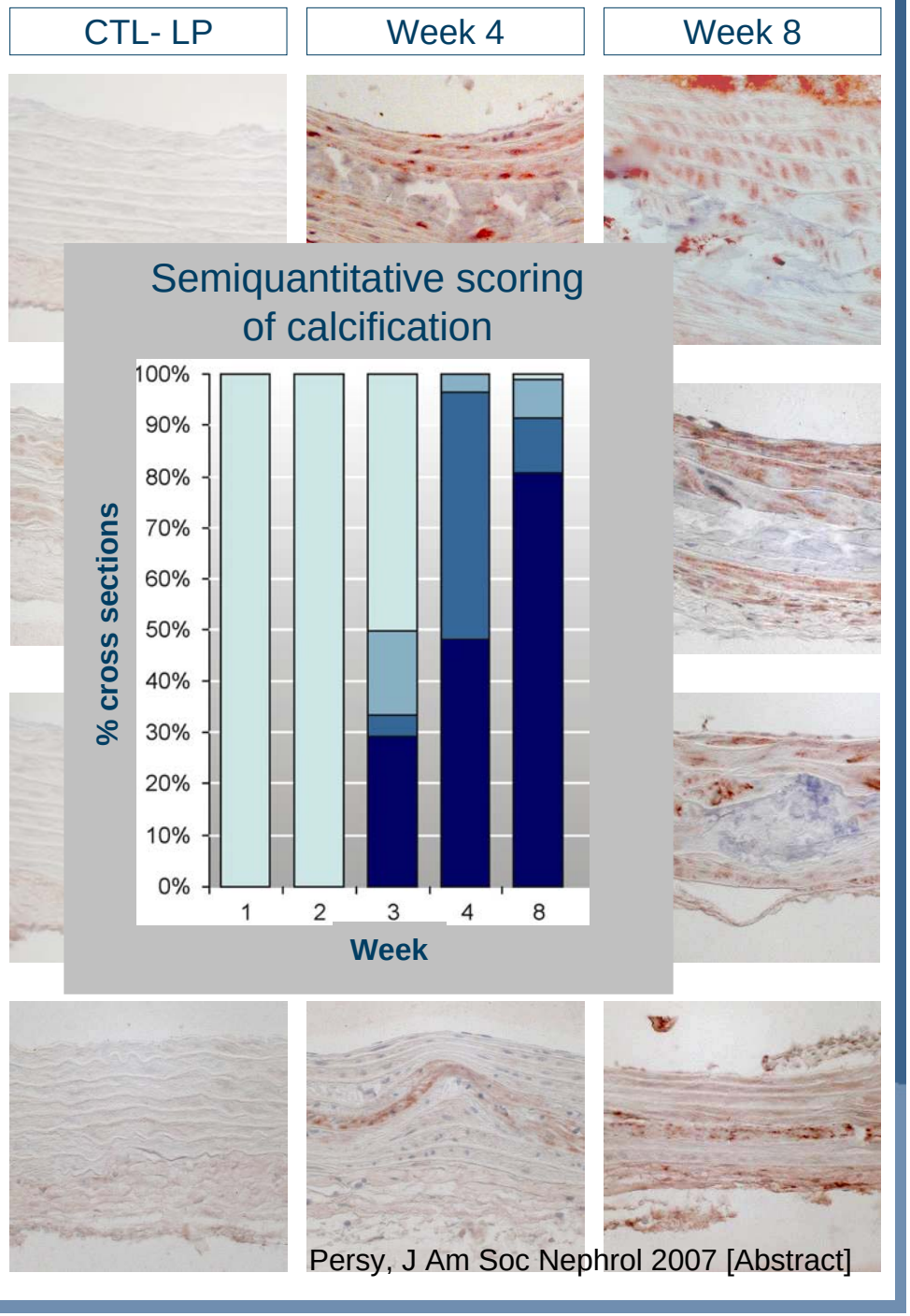






Expression level

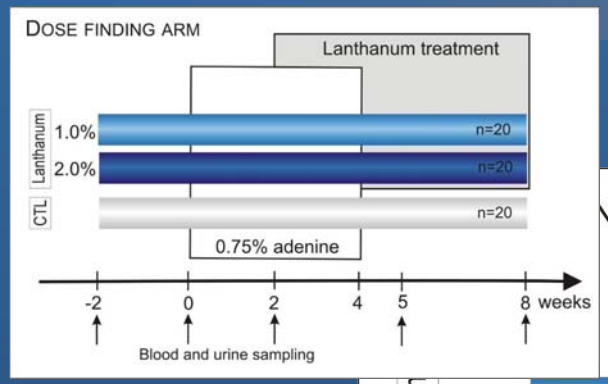
- 3: Global
- 2: Partial
- 1: Focal
- 0: None

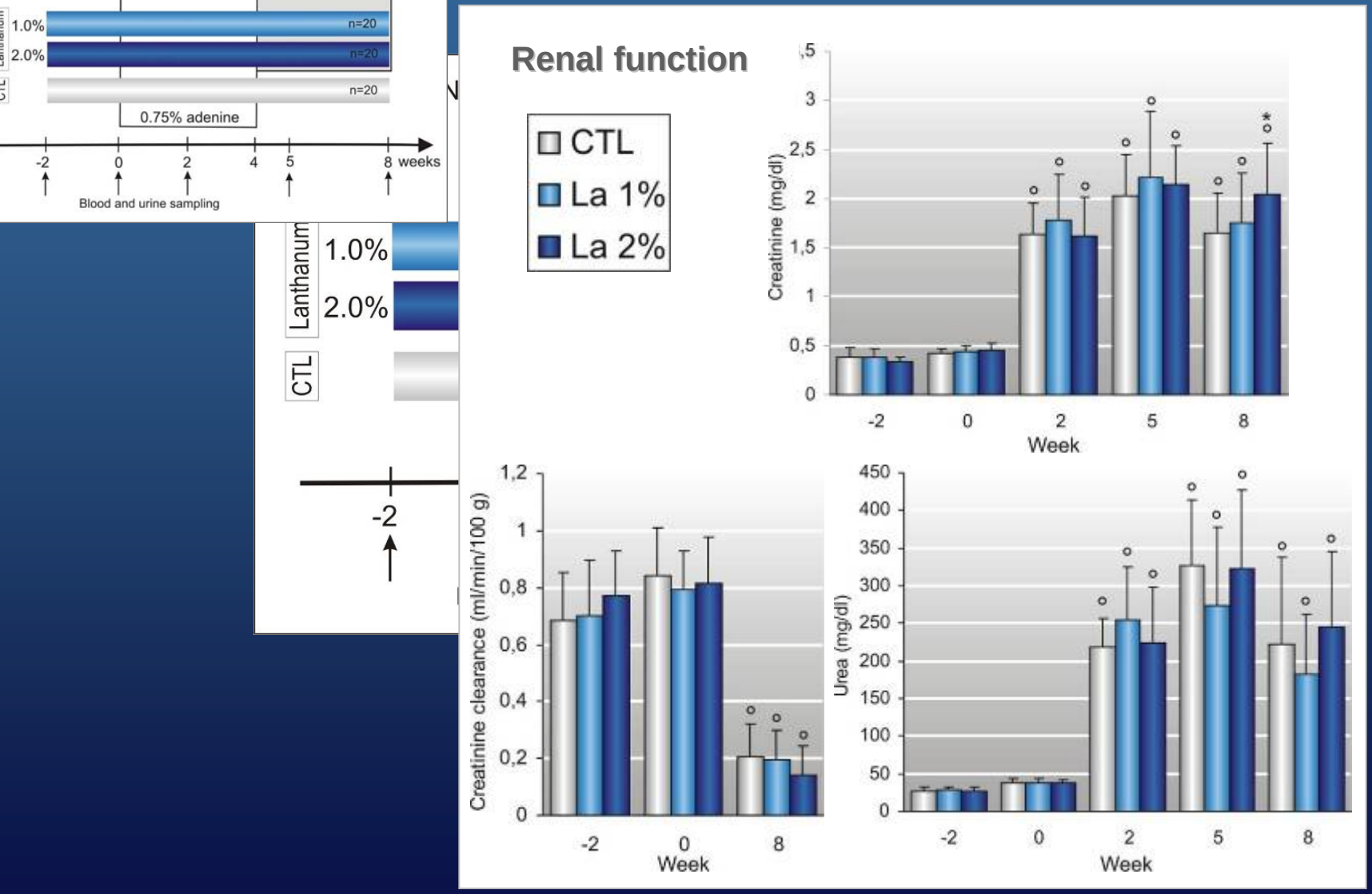


Persy, J Am Soc Nephrol 2007 [Abstract]

Intervention

Effect of La on uremia-related vascular calcification

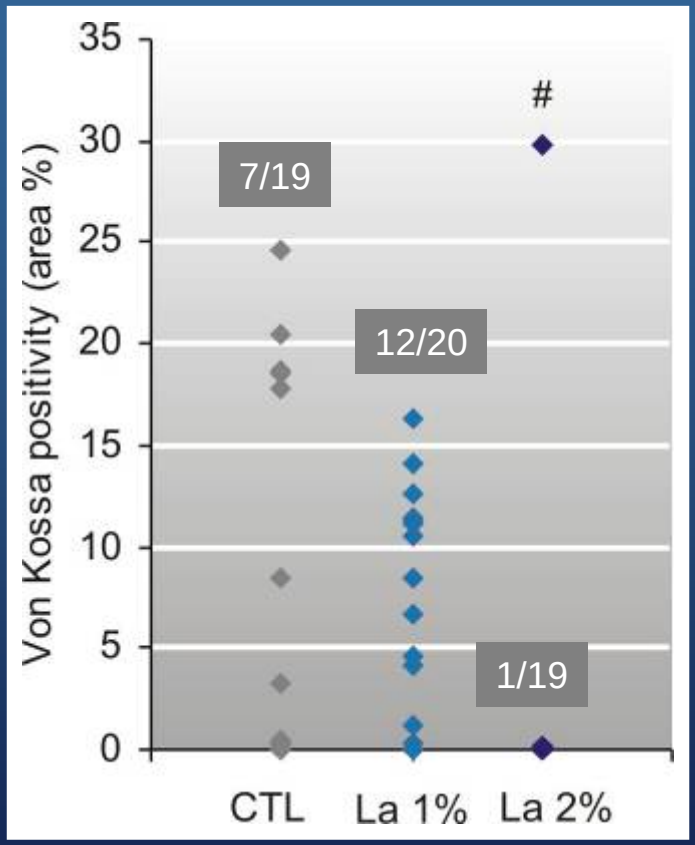




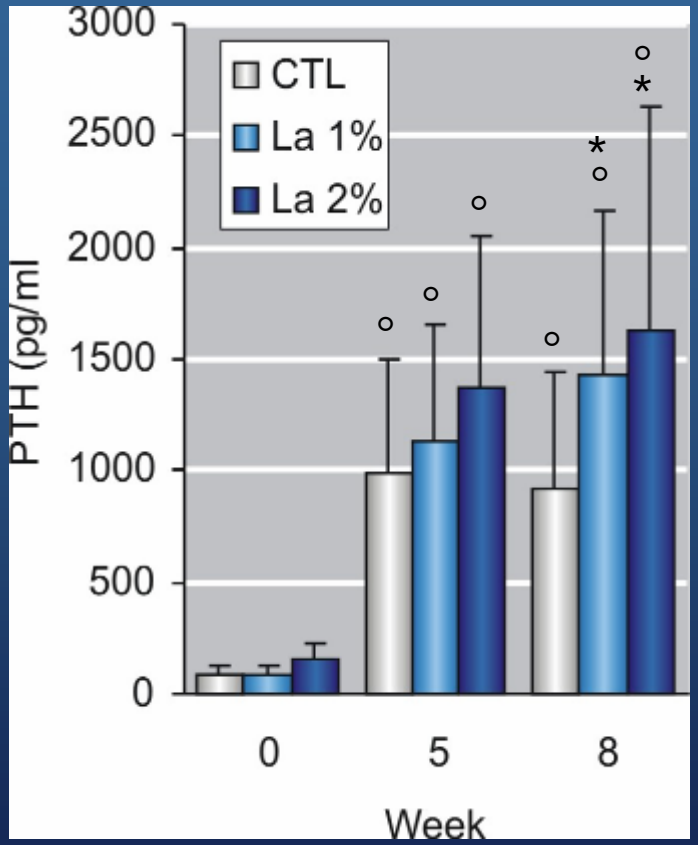
Neven NDT 2009

°: p<0.05 vs. week 0
*: p<0.05 vs CTL

Effect of lanthanum carbonate on adenine induced vascular calcification



#: p<0.05 vs. La 1%



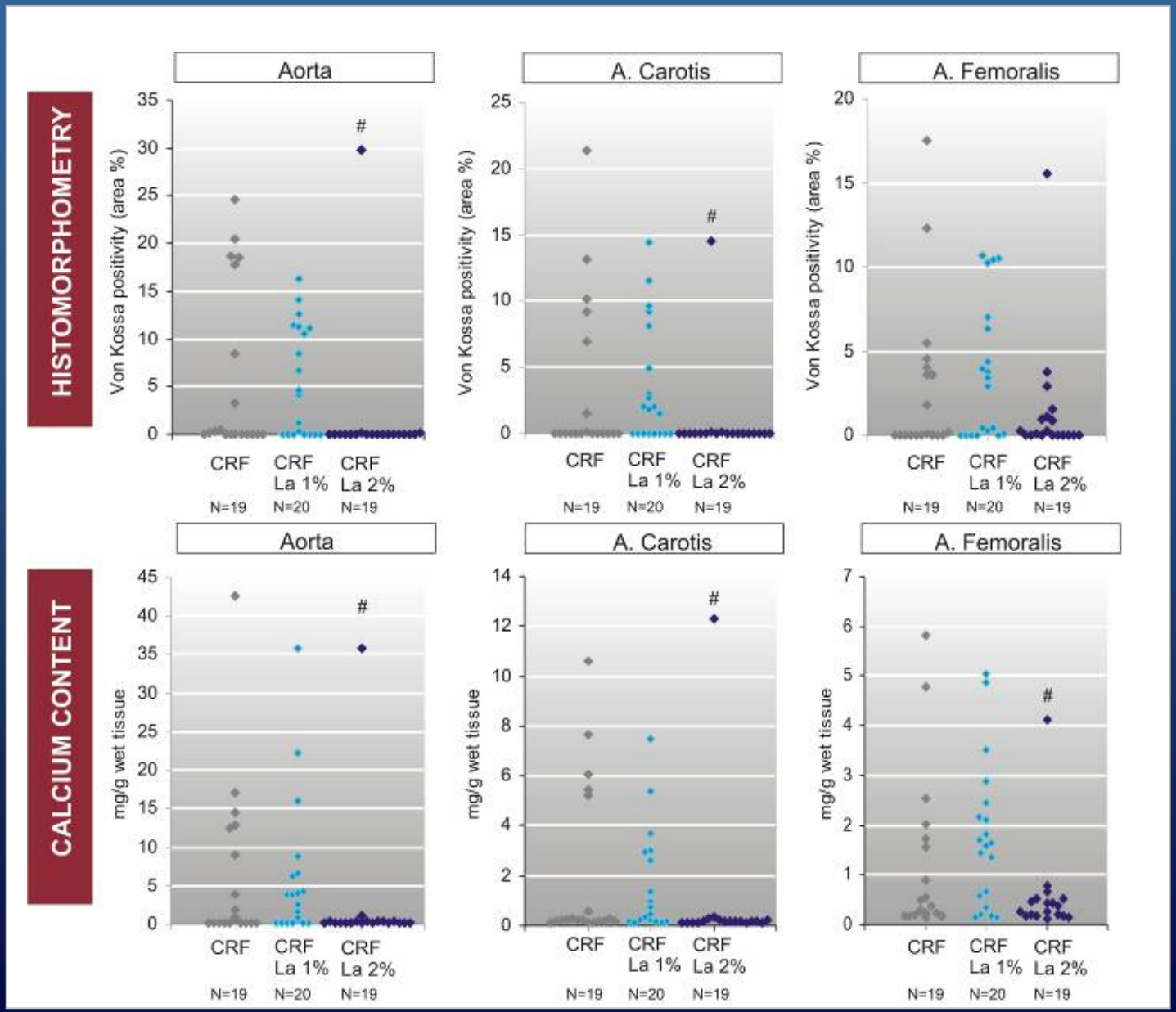
°: p<0.05 vs week 0; *: p<0.05 vs CTL

Neven et al. 2009 NDT Jan)

Intervention

Effect of La on uremia-related vascular calcification

Vascular calcification

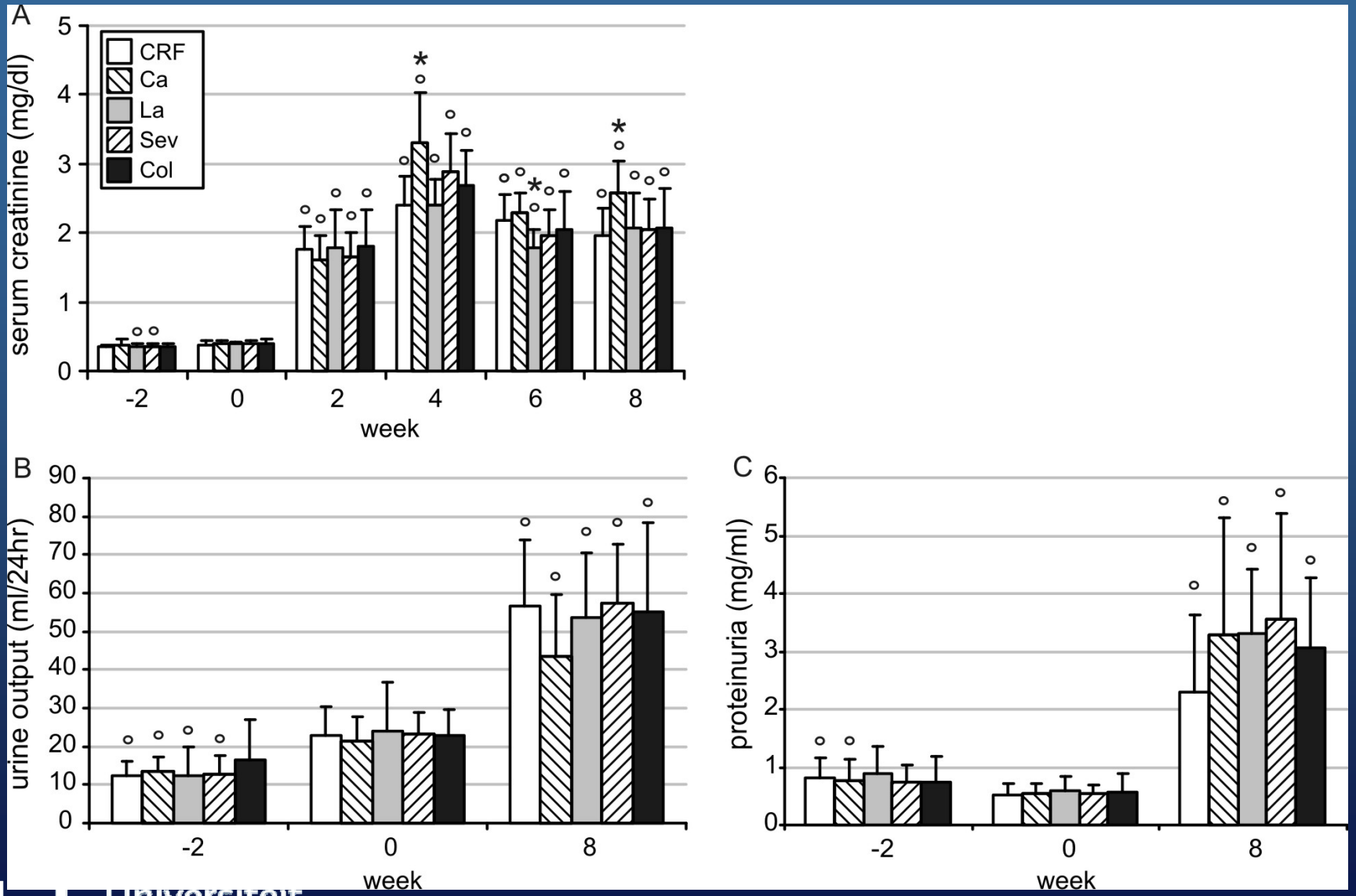


Osterix

Sox9

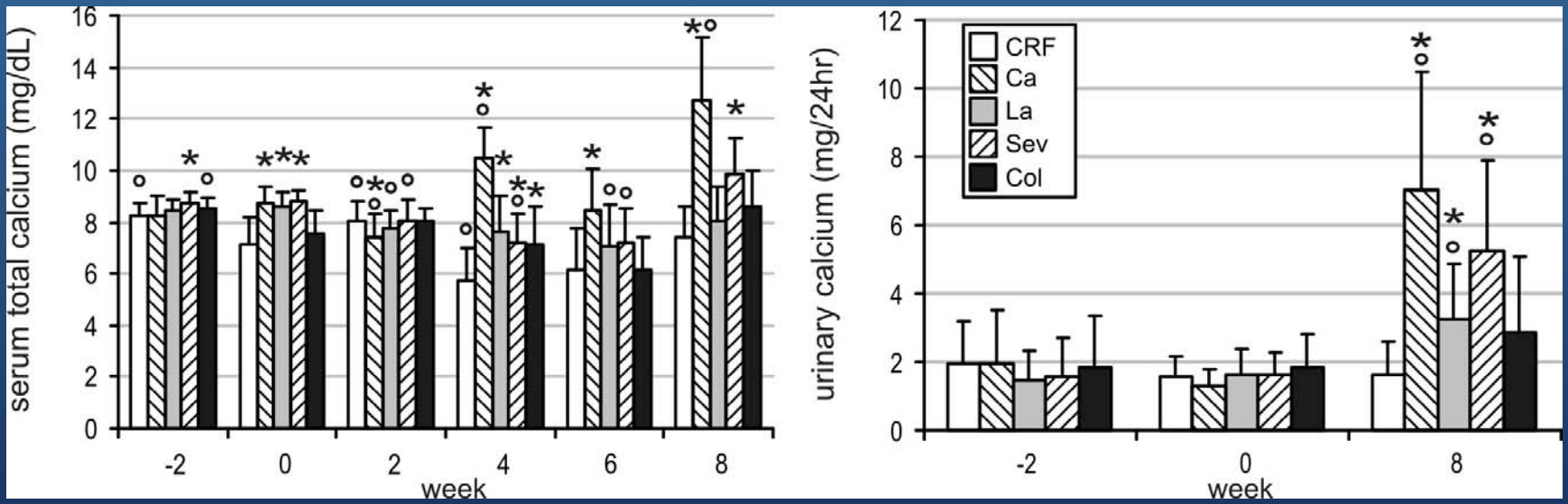
#: p<0.05 vs. La 1%

NDT 2009



° p<0.05 versus week 0

* p<0.05 versus untreated CRF group at the same time point



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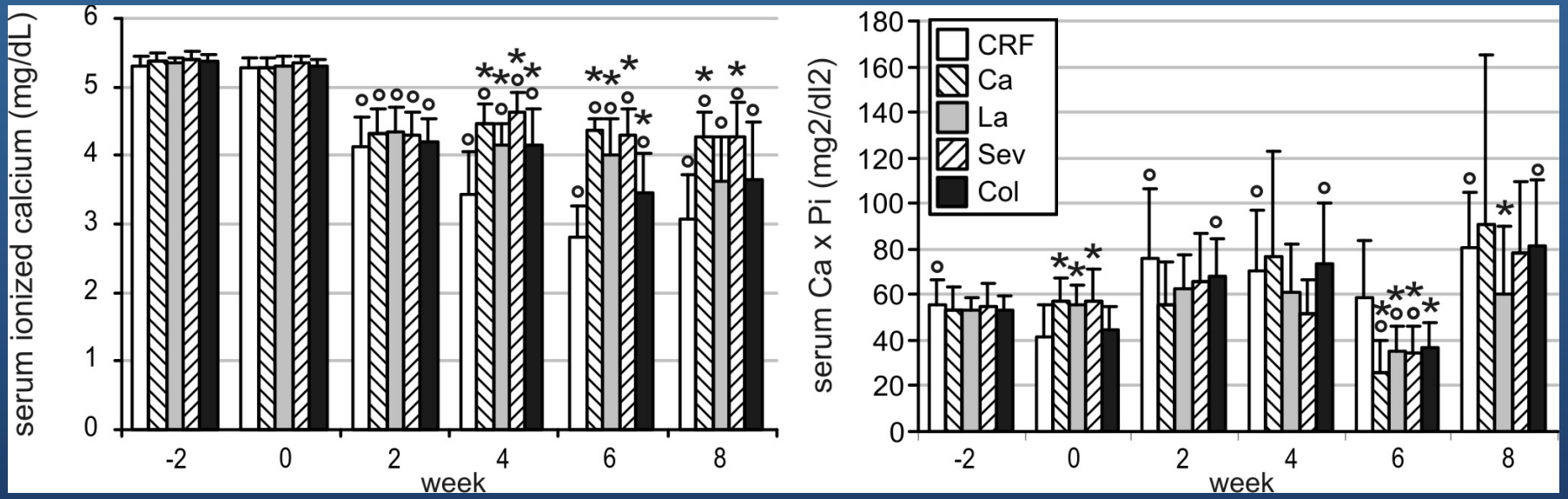
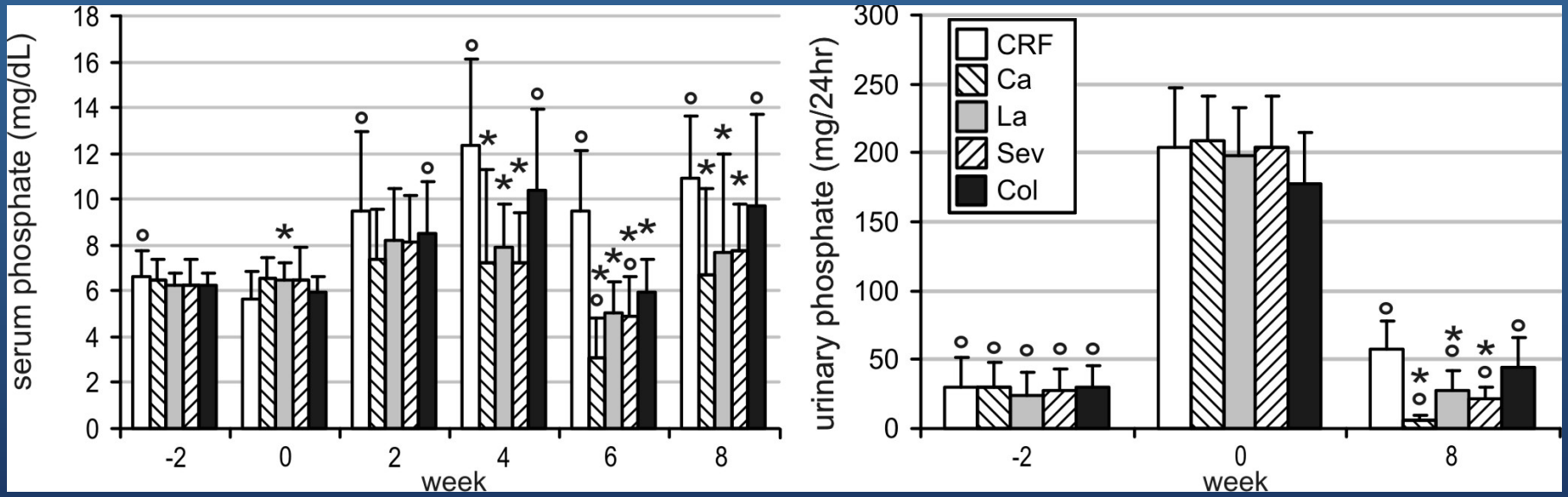


° p<0.05 versus week 0

* p<0.05 versus untreated CRF group at the same time point



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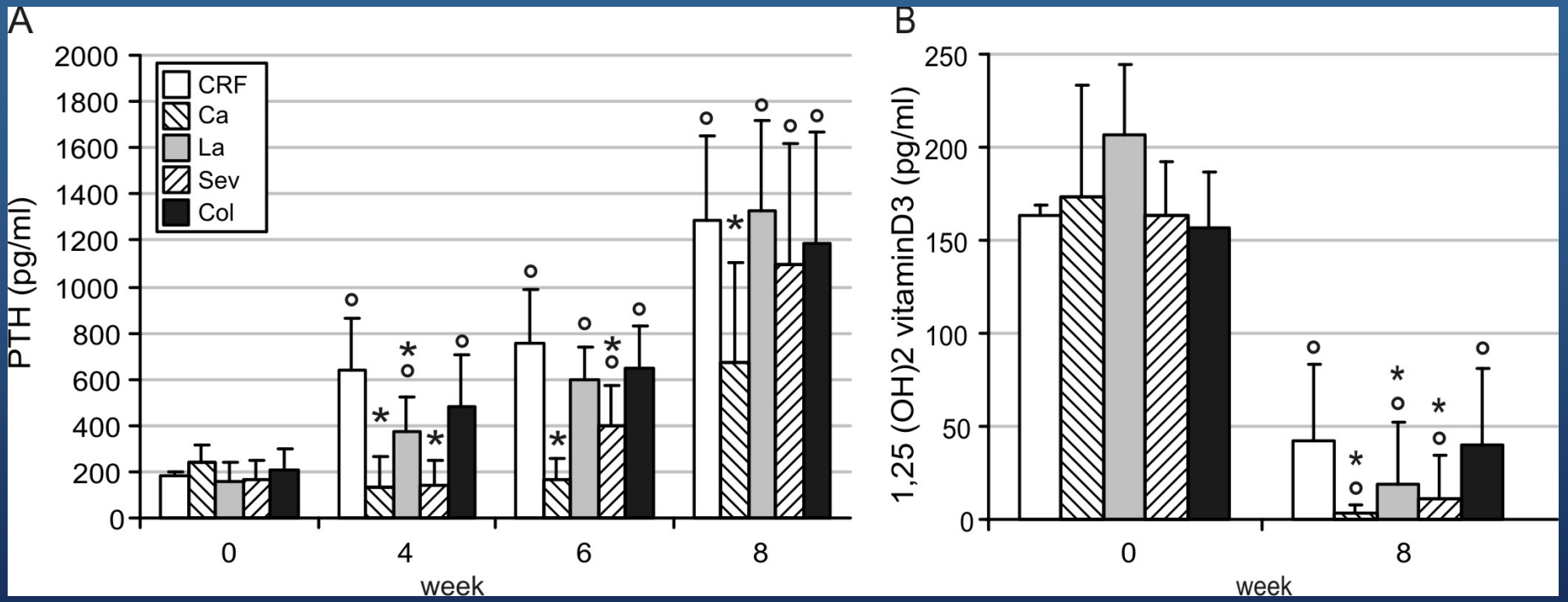

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