Uraemic vascular damage and calcification in children on dialysis

Prevention vs damage limitation?

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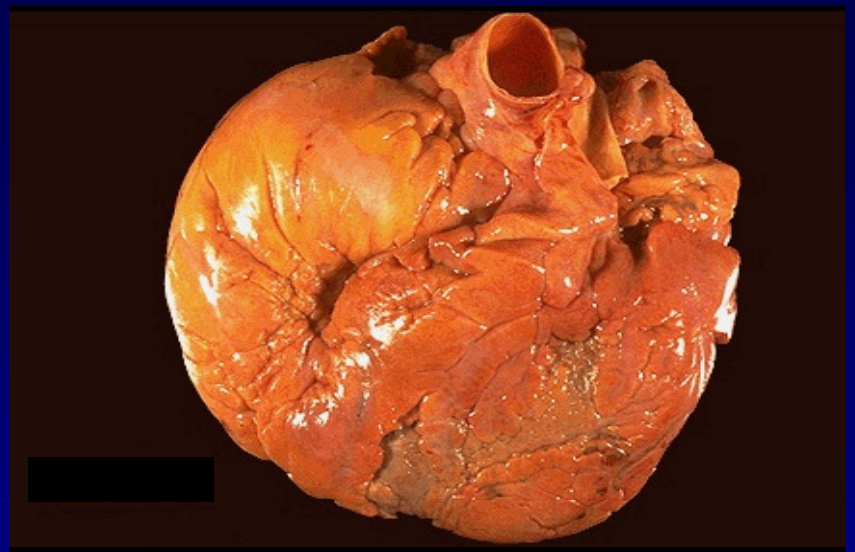
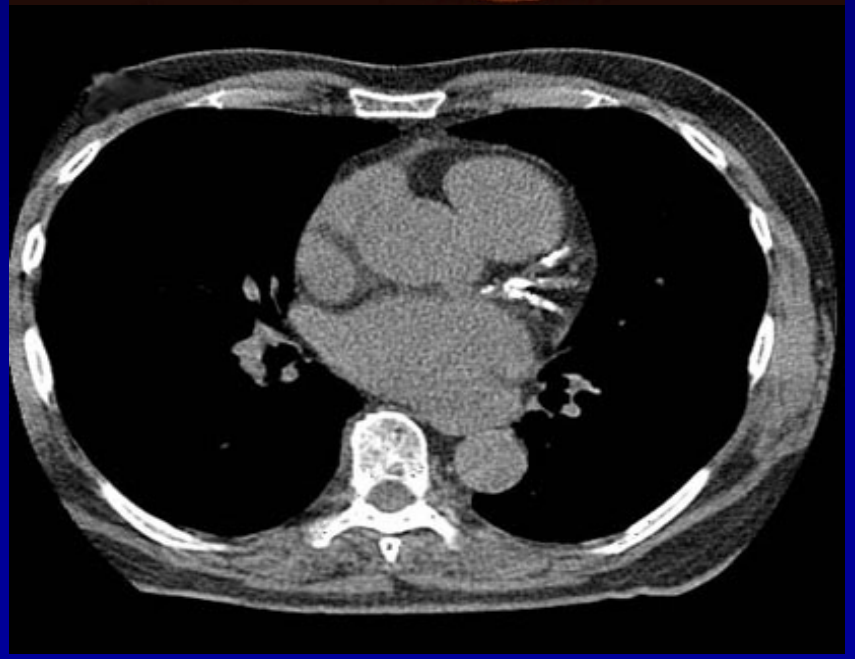
Cardiovascular disease in children – does it happen?



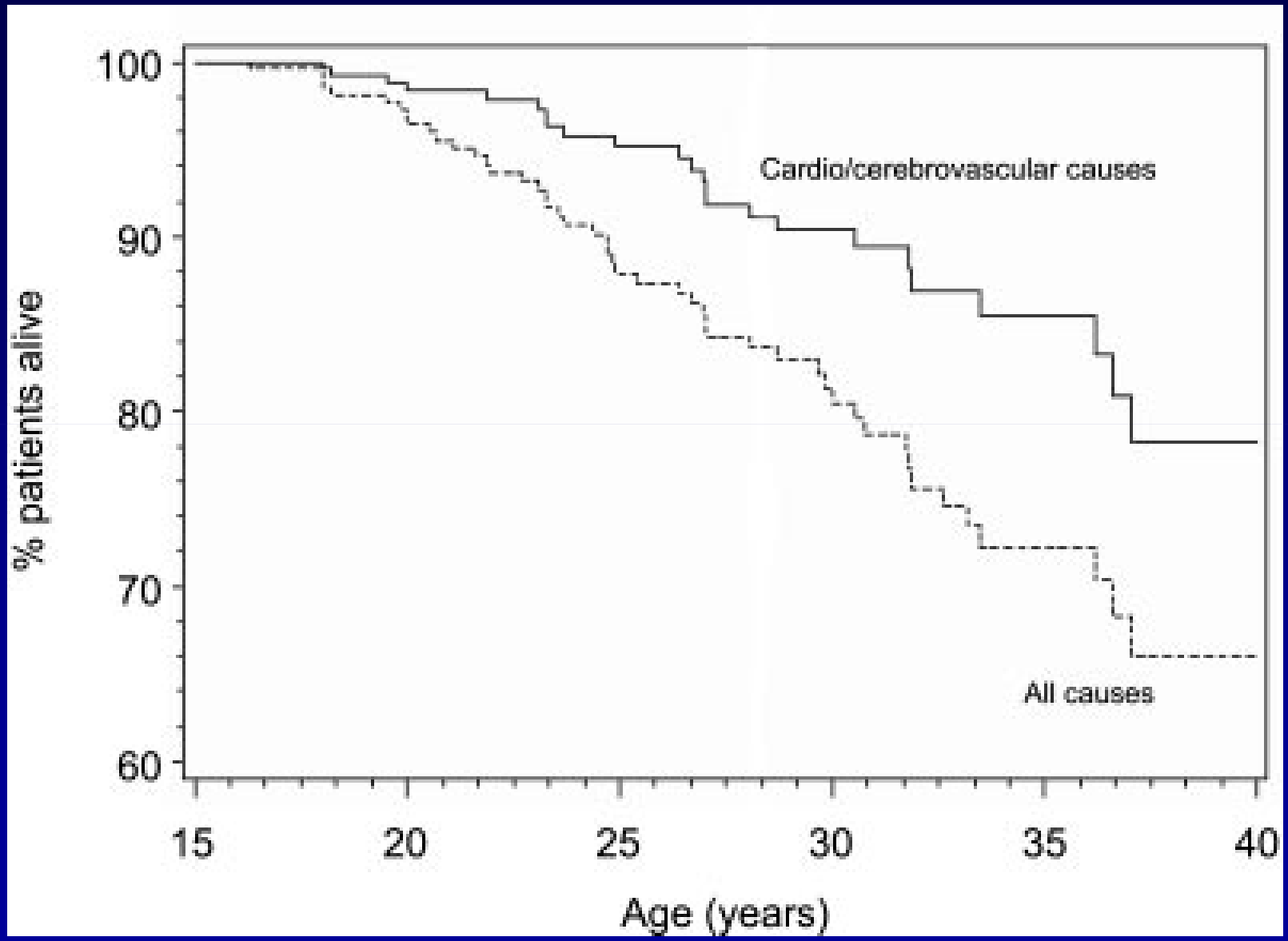


Outline

- CVD in childhood CKD
  - epidemiology
  - when does it begin?
- What is the nature of the vascular damage?
  - Risk factors
  - Clinical studies
- Is there direct evidence of vascular damage and calcification?
  - Clinico – pathological correlations

The role of Ca and P in vascular injury

Mortality in childhood-onset CKD



Oh et al, Circulation, 2002

CVD is the most common cause of death in childhood CKD

US

- 38% deaths were from CVD *Chavers et al, KI 2002*

Dutch cohort study

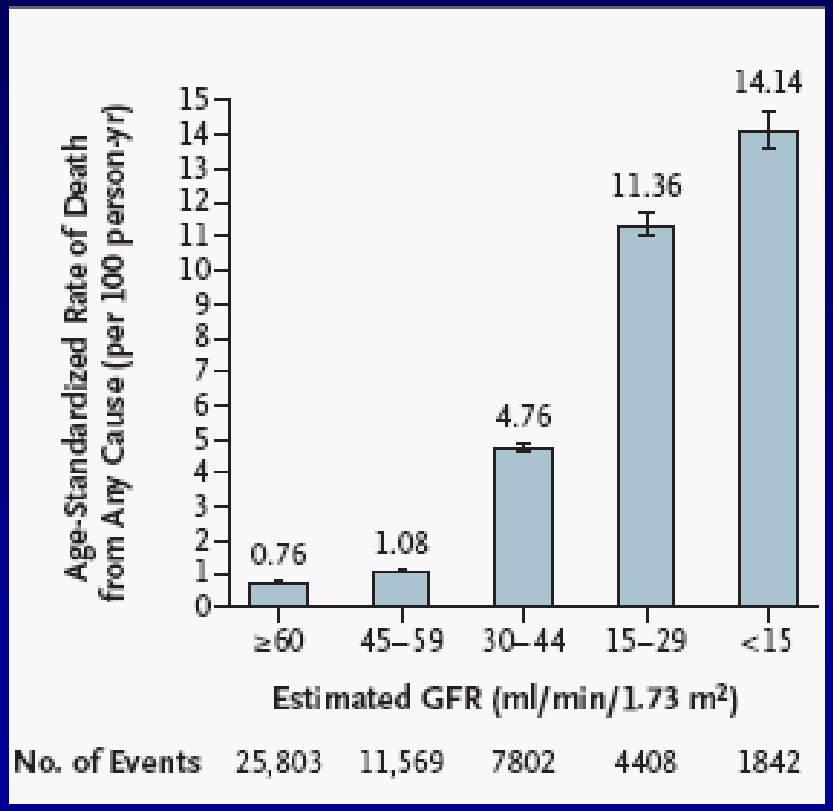
- 24% deaths due to CVD / cerebrovascular disease

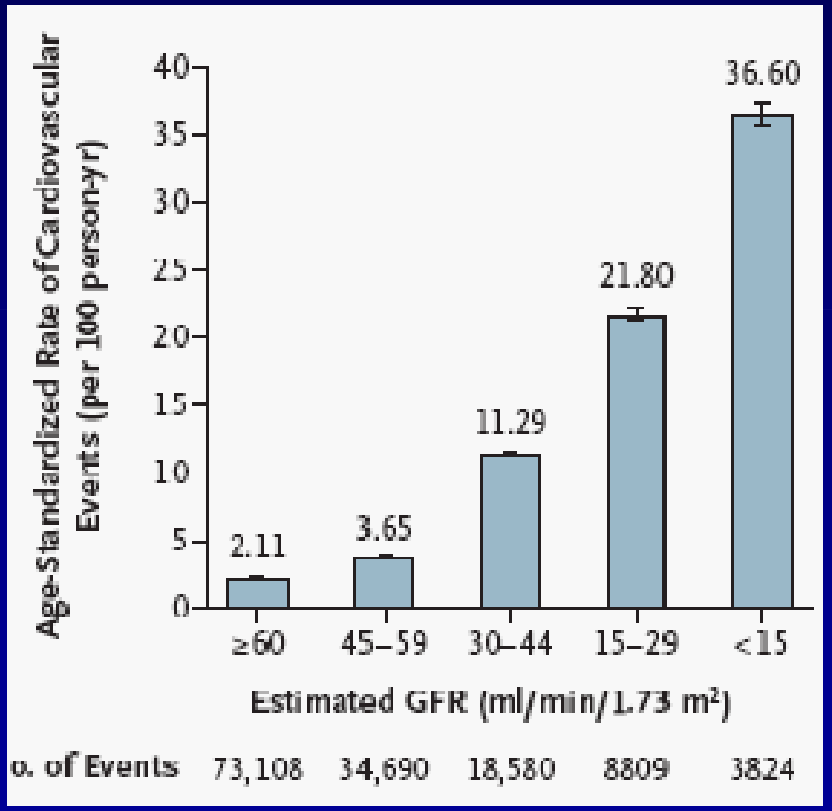
Groothoff et al, KI 2002

ANZDATA

- 57% deaths on HD and 43% on PD are due to cardiac causes *McDonald et al, NEJM 2004*

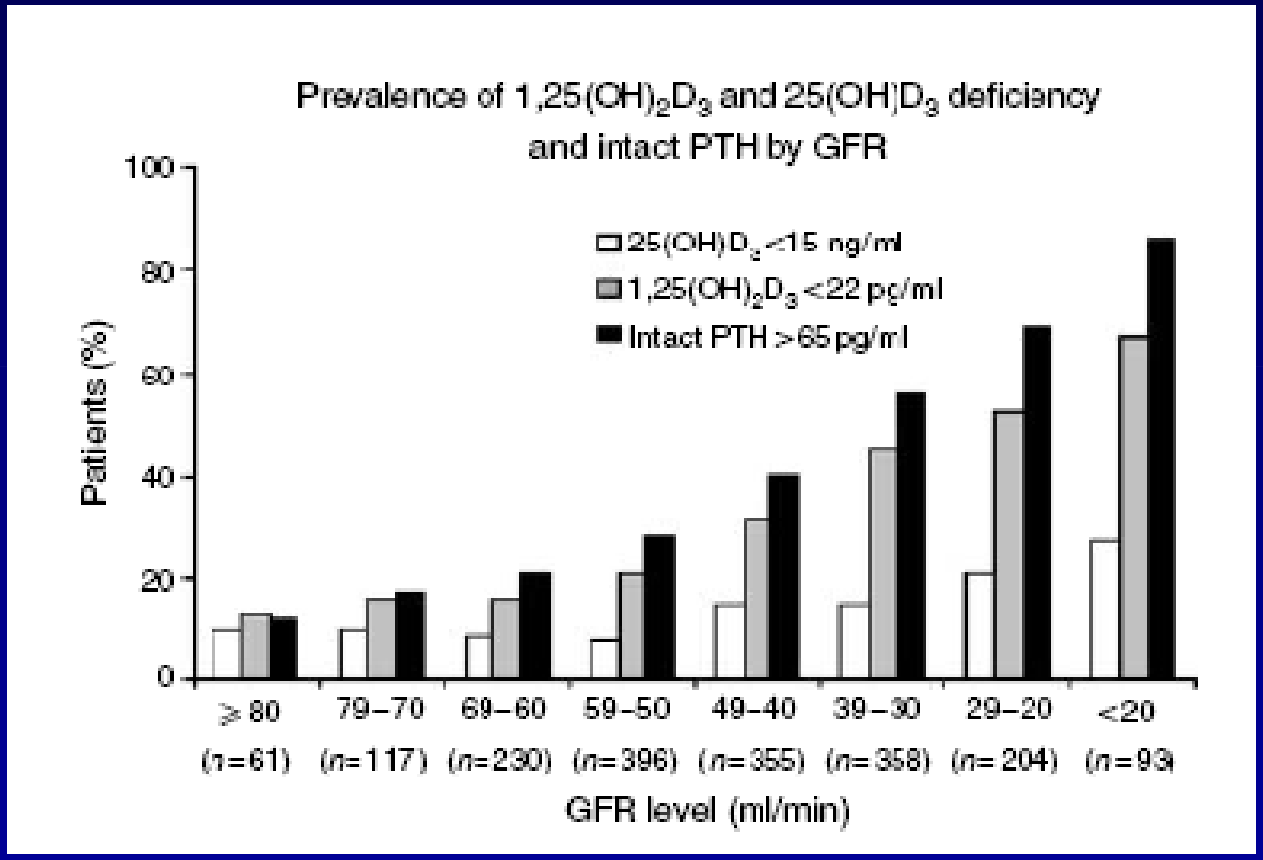
There is an independent and graded association between GFR and CVD





Go et al, NEJM; 2004

Metabolic disturbances in early CKD



Levin et al, KI; 2007

GFR 90

↑ FGF-23

↓ Vitamin D

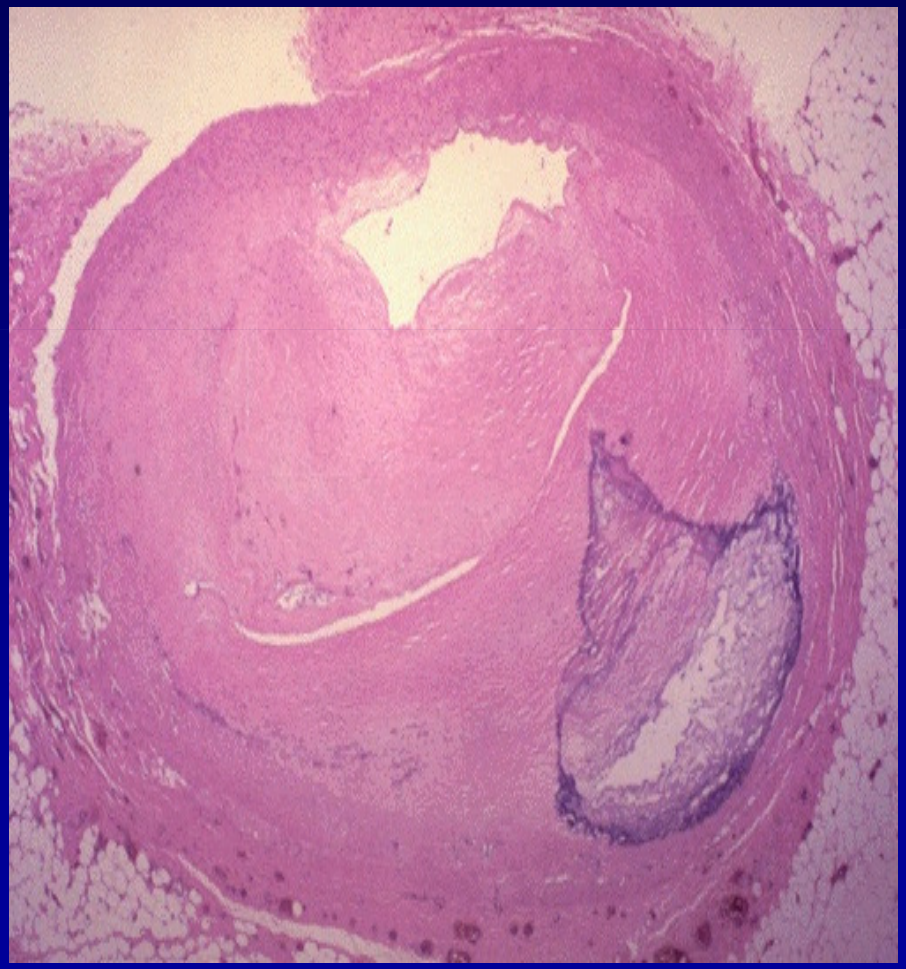
↑ PTH

↑ Ca x P

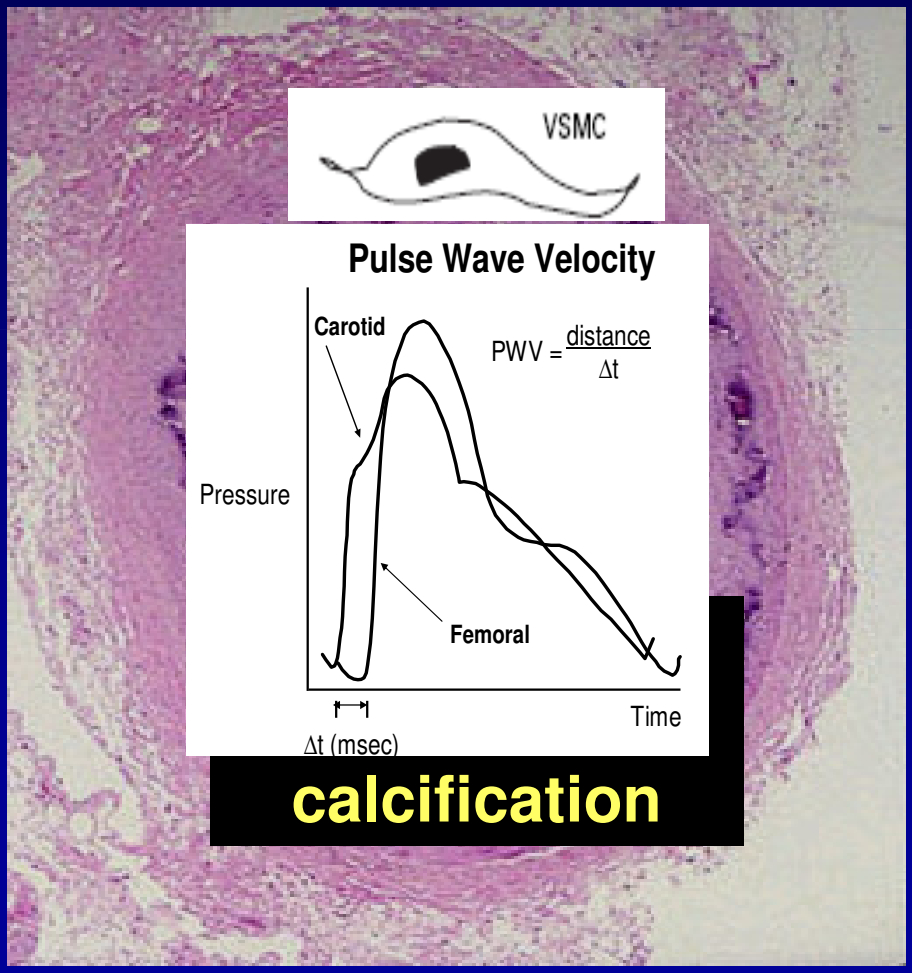
Dialysis

Arterial Medial Calcification in CKD

Atherosclerosis



Arteriosclerosis



Adapted frm London et al, NDT 2002

Risk factors for vascular injury

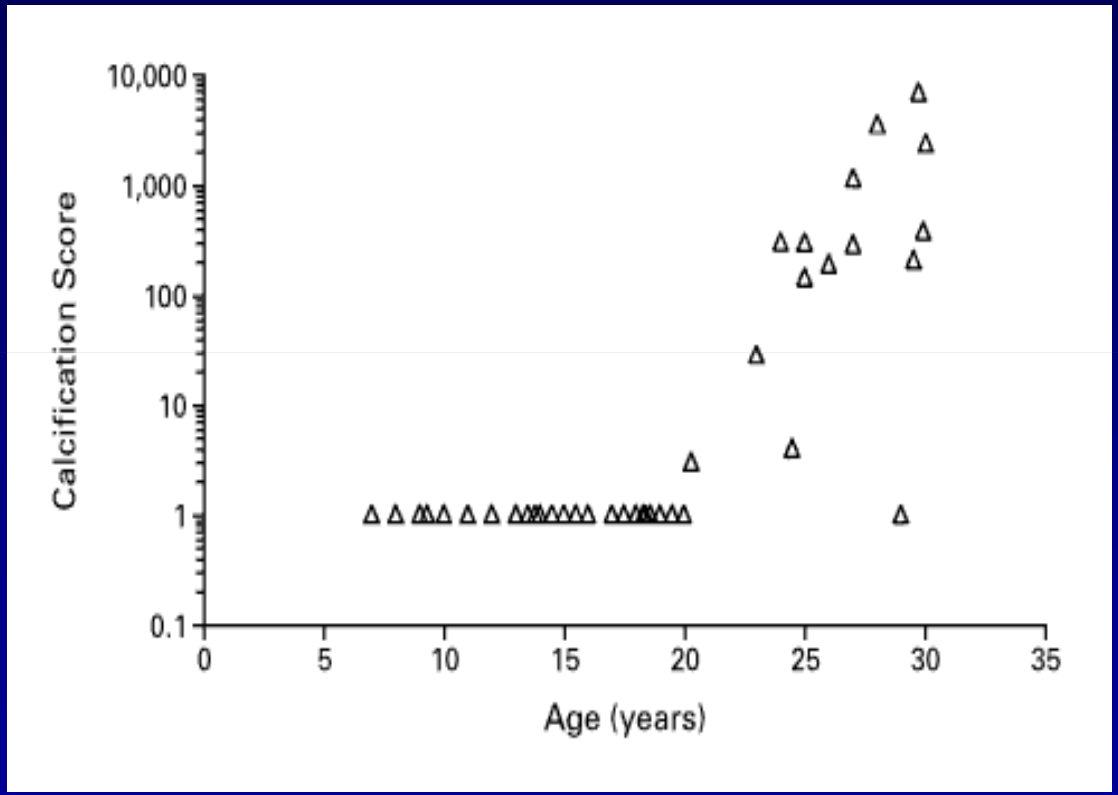
'Traditional' risk factors

- Hypertension
- Diabetes
- Hypercholesterolemia
- Dyslipidemia
- Insulin resistance
- Obesity
- Smoking
- Male gender
- Family history of CVD

Risk factors in CKD

- Abnormal Ca & Phosphate
- Hyperpapathyroidism
- ? Vitamin D analogues
- Chronic fluid overload
- Inflammation
- Oxidative stress
- Hyperhomocysteinemia
- Albuminuria
- Malnutrition
- Perturbation in physiological inhibitors (fetuin-A, OPG)
- Abnormal FGF-23 levels

Clinical studies in children – key papers



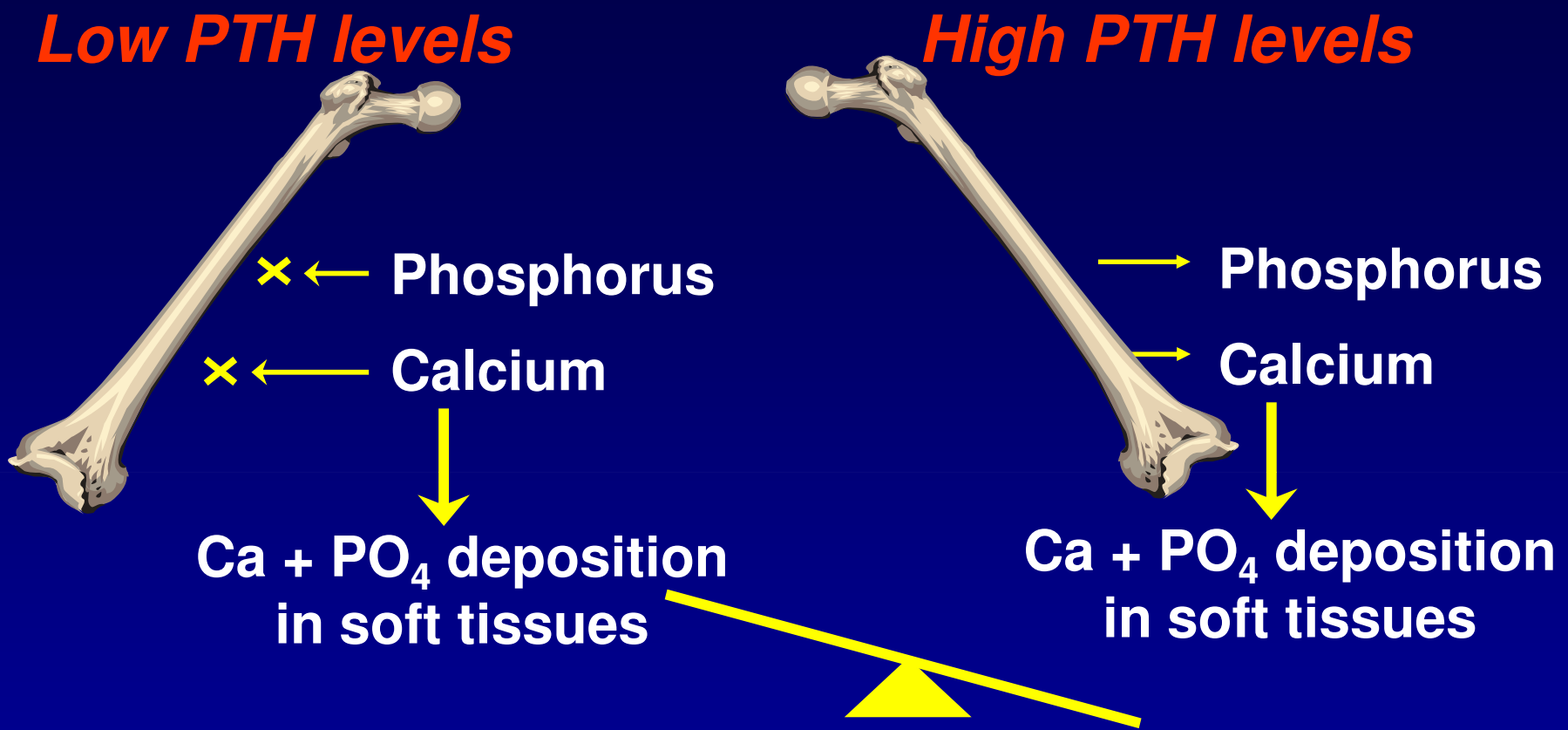
Patients with calcification were:

- older
- longer dialysis vintage
- Higher P & CaxP
- Higher Ca intake from binders

Goodman et al, NEJM, 2000

Authors / Journal	Number of dialysis pts	Vascular measures	Clinical / biochemical associations
Oh / Circulation 2002	39	cIMT CAC	- dialysis duration - mean serum Ca x P - PTH levels
Litwin / JASN 2005	37	cIMT	- dialysis duration - mean serum Ca x P - Mean calcitriol dose
Mitsnefes / JASN 2005	16	cIMT distensibility	- dialysis duration - mean serum Ca x P - Mean calcitriol dose - mean PTH levels
Shroff / JASN 2007	85	cIMT PWV CAC	- dialysis duration - mean serum Ca x P - Mean calcitriol dose - mean PTH levels
Civilibal / Ped Nephrol 2007	37	cIMT FMD ECHO	- mean serum Ca x P - total & LDL cholesterol - mean calcitriol dose

PTH levels and vascular outcome



	CKD 3 - 4	Dialysis
KDIGO	unknown	2 - 9 times ULN
European guidelines	Normal range	2 – 3 times ULN

Is high PTH a risk factor for CVD?

Inclusion criteria

Children on dialysis who are:

- 5 – 18 years old
- Dialysis for ≥ 6 months
- CKD Stage IV for ≥3 years

Exclusion criteria

- Underlying inflammatory disease eg vasculitis
- Diabetes mellitus
- Uncontrolled hyperlipidaemia
- Uncontrolled hypertension
- Smokers

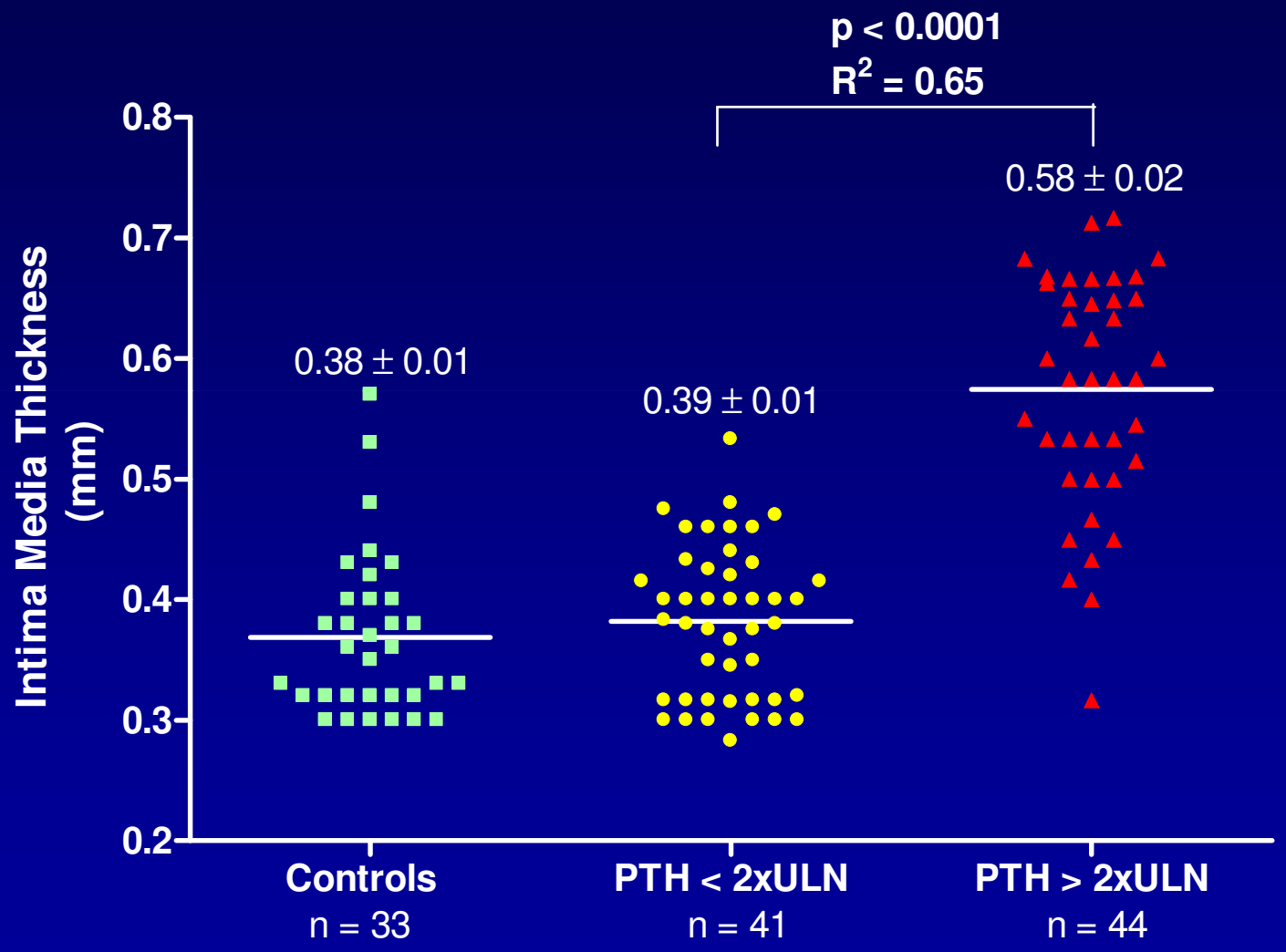
Based on mean time-integrated PTH levels –

Group I - PTH ≤ 2x ULN [n = 41]
Group II - PTH > 2x ULN [n = 44]

Matched for confounders

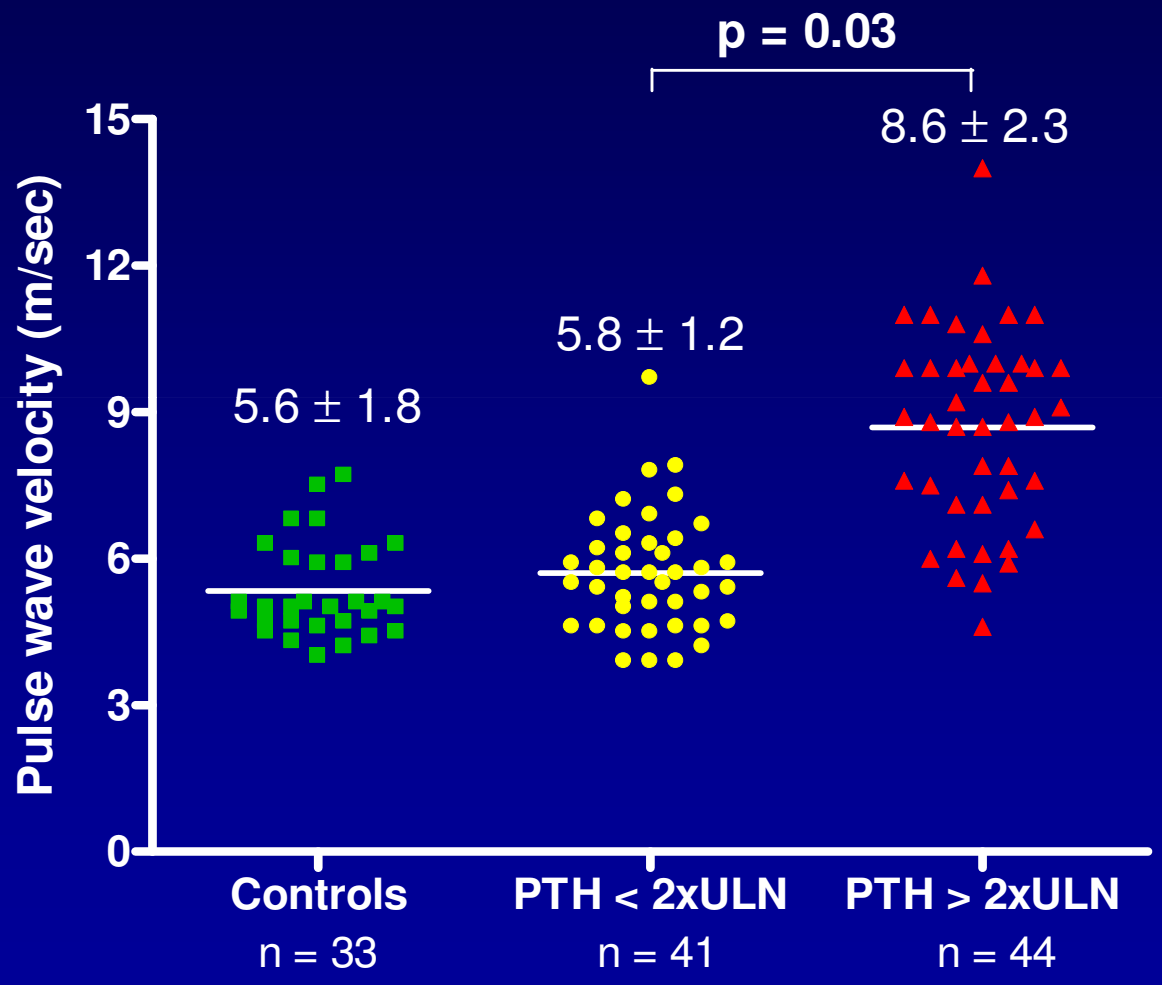
Shroff et al, JASN 2007

Increased cIMT is associated with high PTH levels



Shroff et al, JASN 2007

Arterial stiffness is associated with high PTH levels



Shroff et al, JASN 2007

Vascular calcification is associated with high PTH levels

Calcification present in 17/85 (20%) patients

	PTH <2 ULN n = 41	PTH >2 ULN n = 44	p
Total	5 (12%)	12 (27%)	<0.01
Calcification score Median (range)	7.8 (0 – 98)	85.3 (0 – 2039)	0.001

Shroff et al, JASN 2007

Vitamin D as a predictor of cardiovascular damage?

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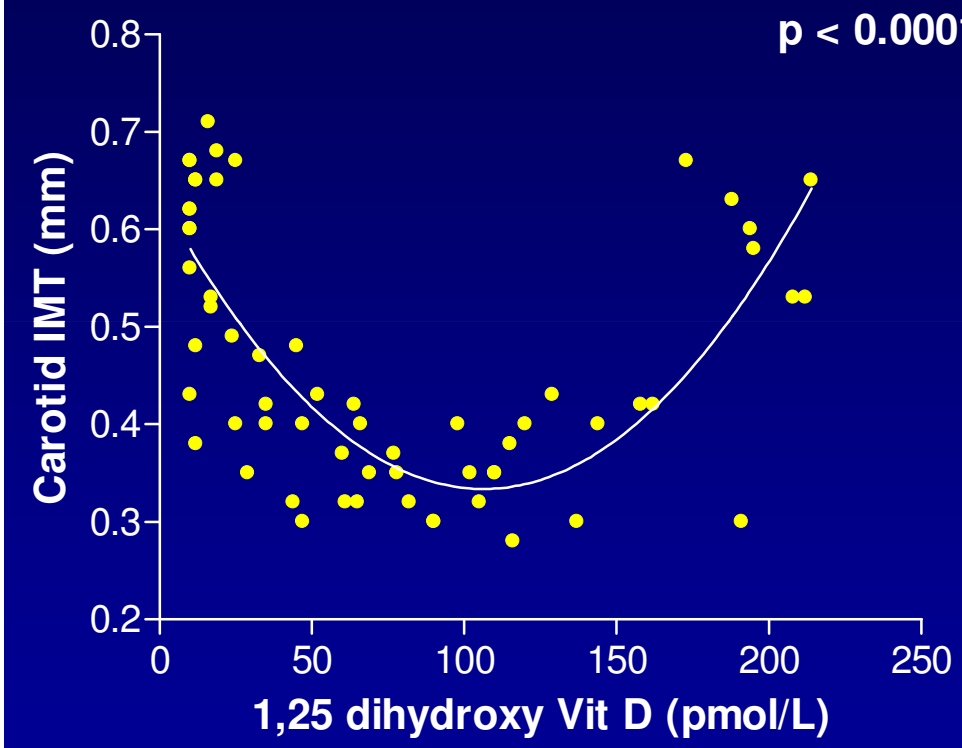
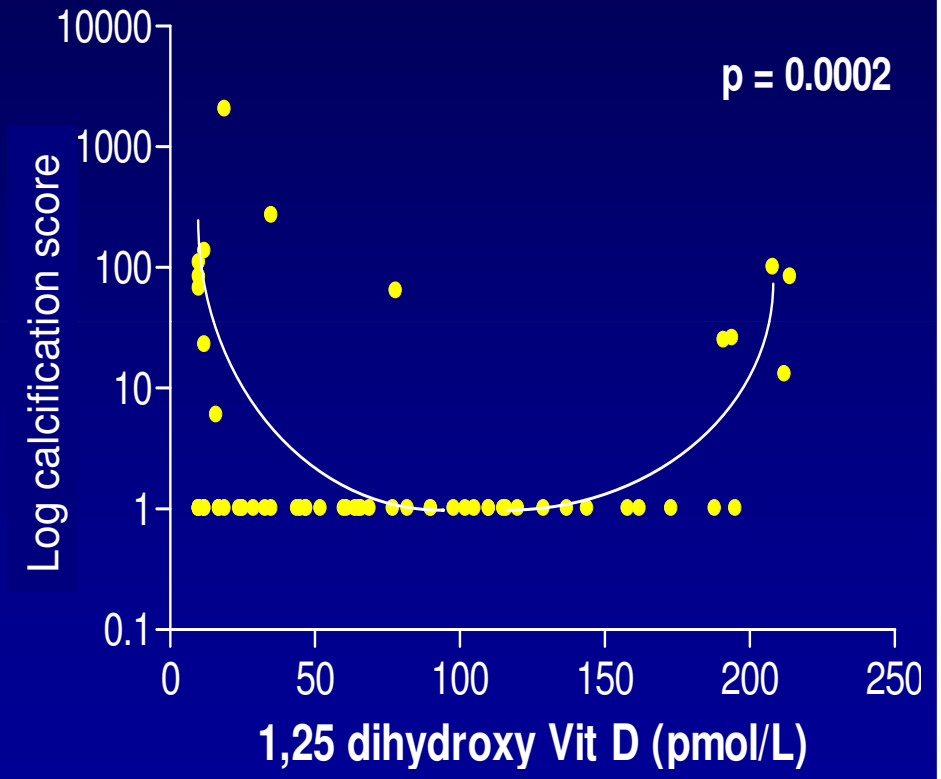
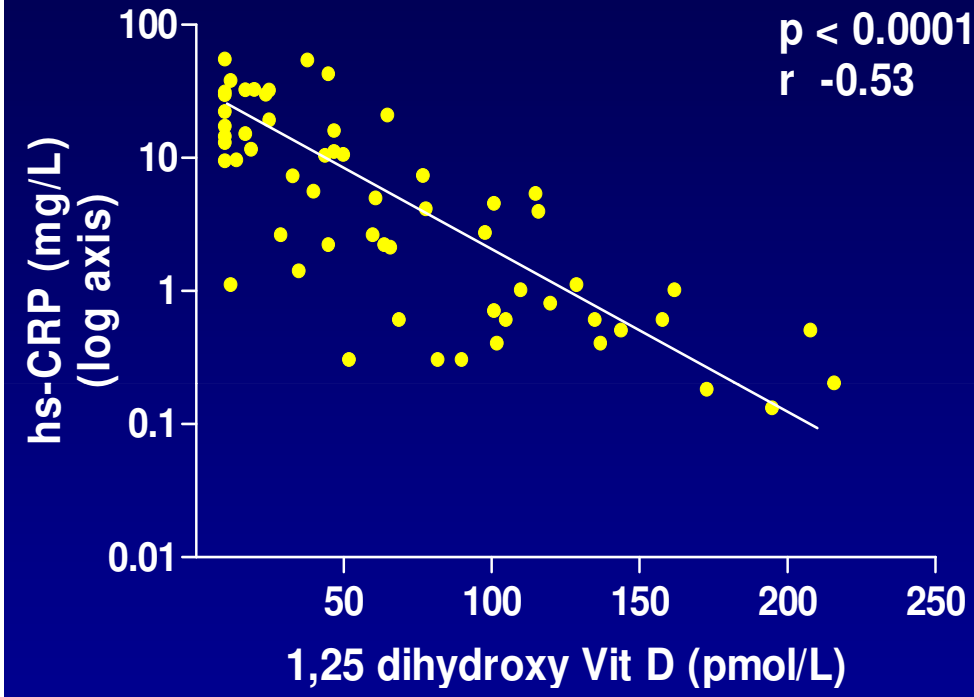
Bimodal effect of 1,25 dihydroxy D

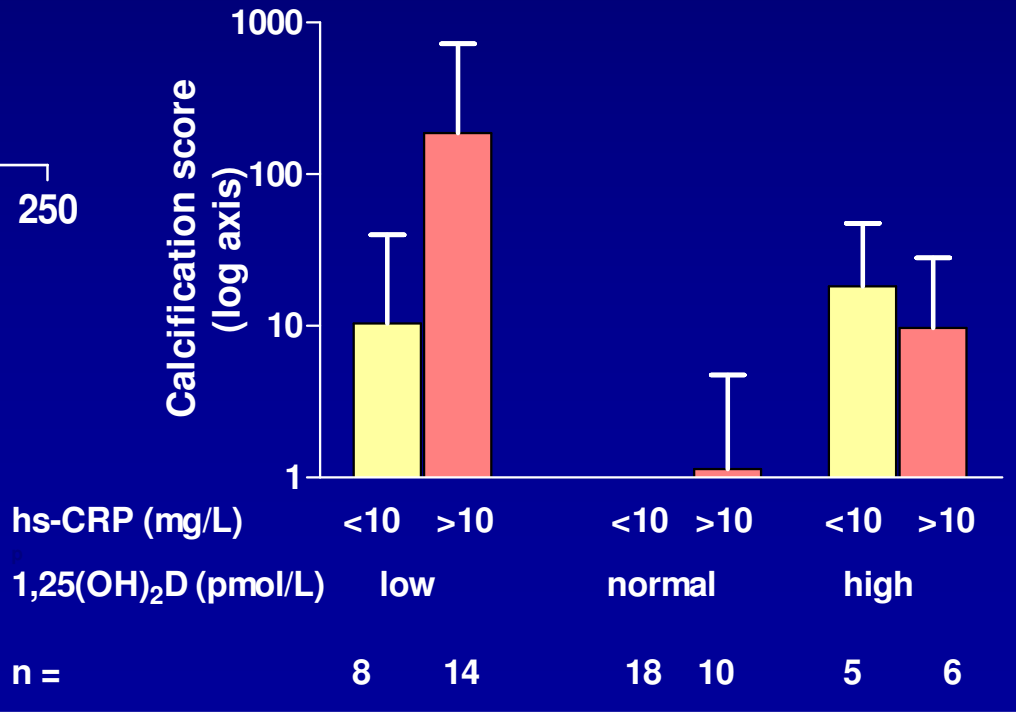




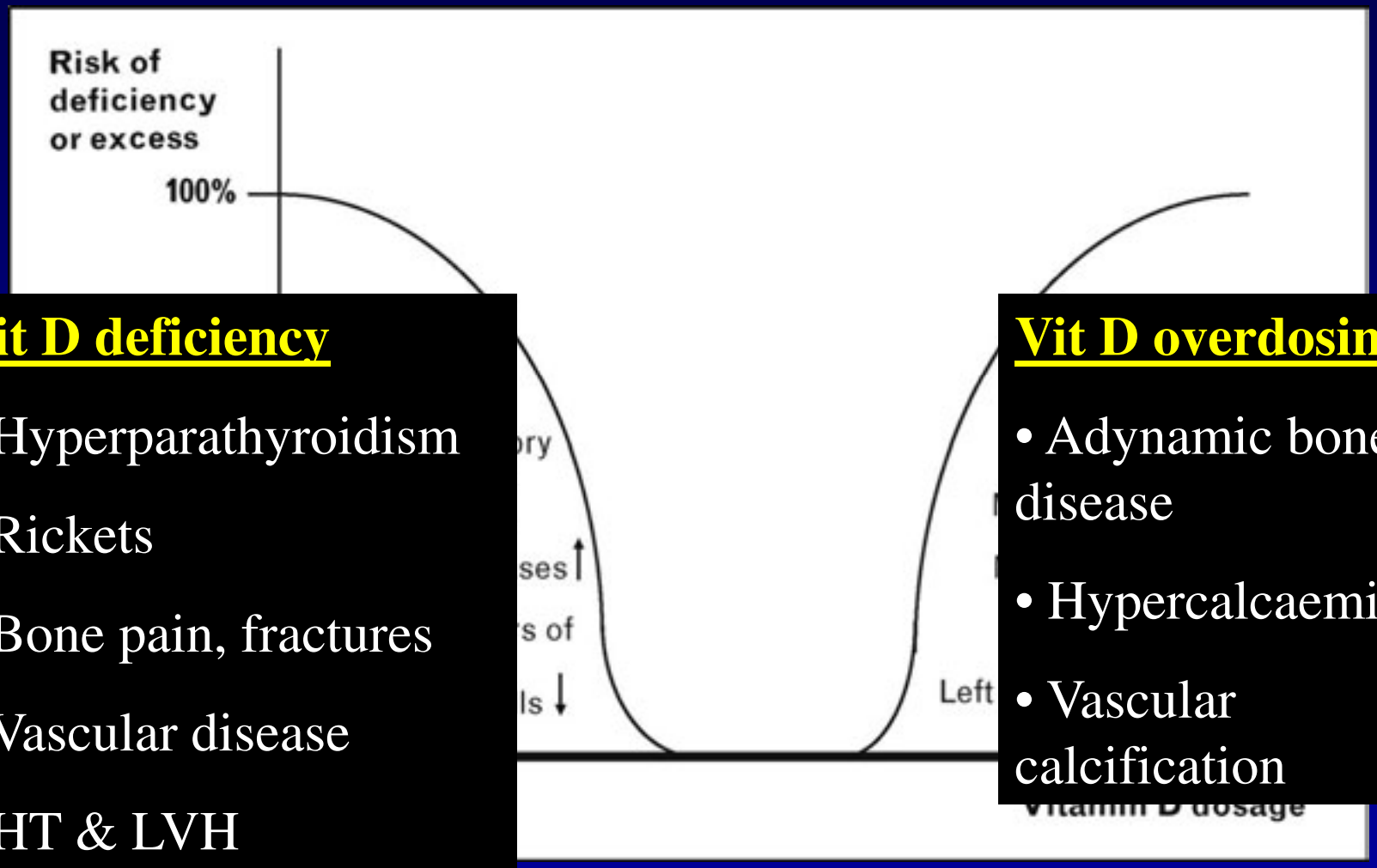
Shroff et al, JASN 2008

The anti-inflammatory effect of Vit D influence calcification





A biphasic dose–response curve for vitamin D on vascular health



Vit D deficiency

- Hyperparathyroidism
- Rickets
- Bone pain, fractures
- Vascular disease
- HT & LVH
- Increased mortality

Vit D overdosing

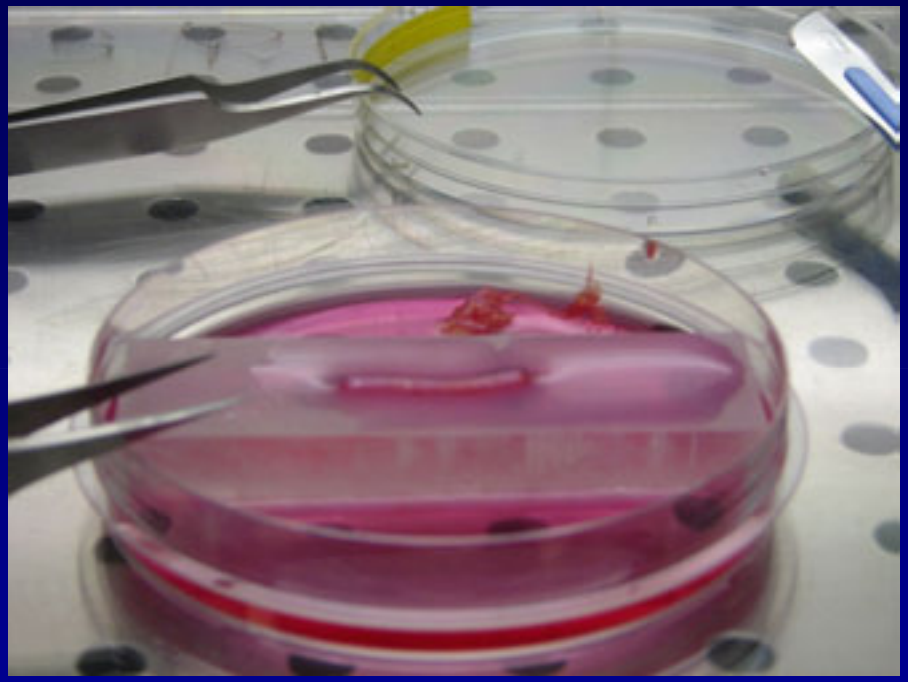
- Adynamic bone disease
- Hypercalcaemia
- Vascular calcification

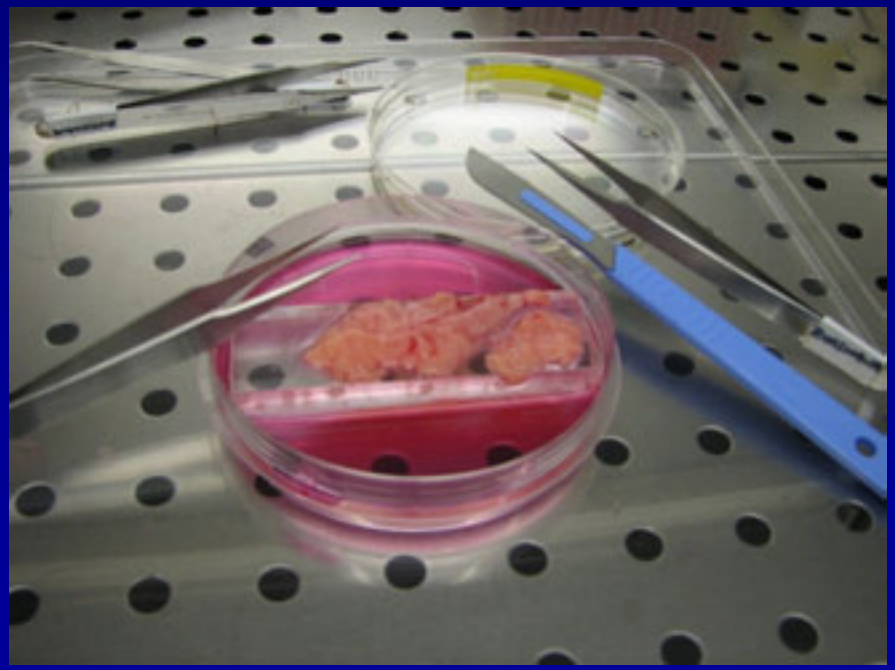
Zittermann A; Curr Opin Lipidol; 2007

Is there direct evidence of vascular damage and calcification in CKD vessels?

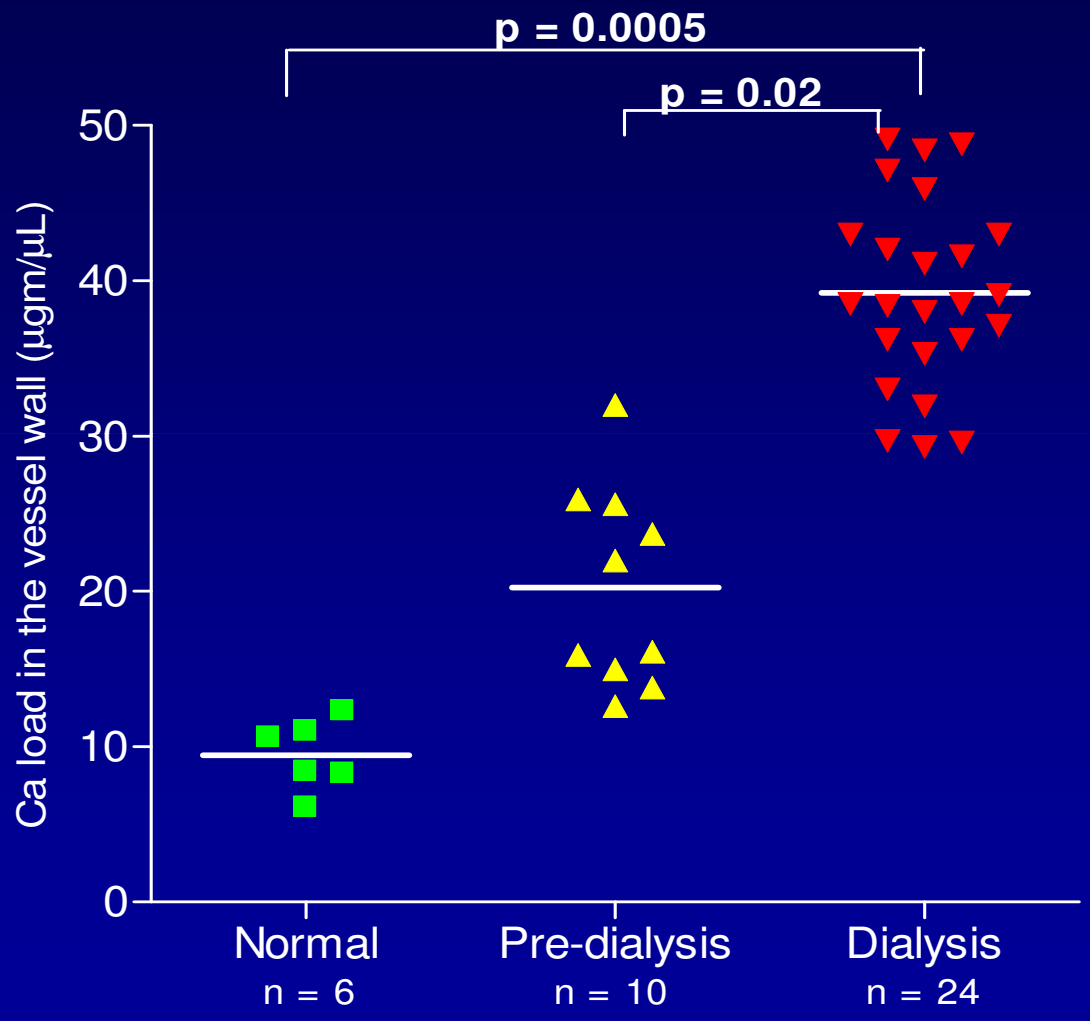
Shroff et al, Circulation, 2008
Shroff et al, JASN, 2010

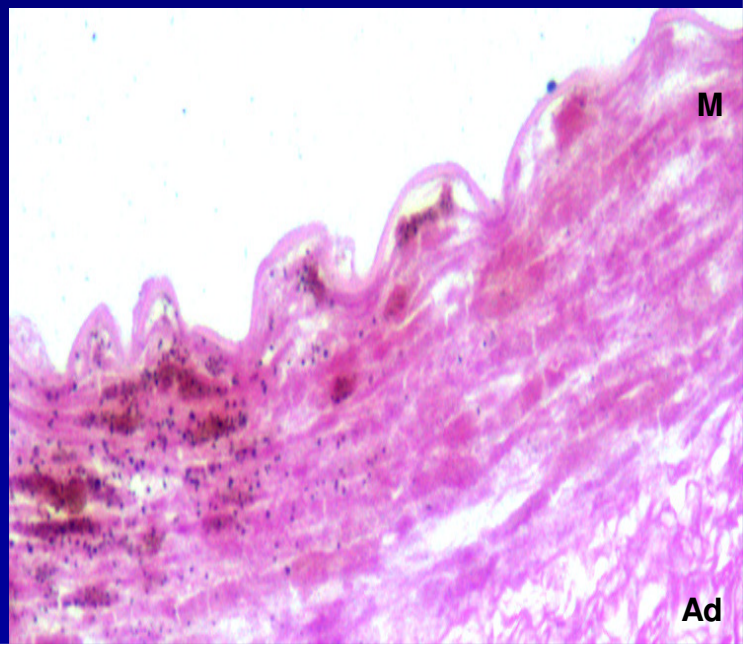
Ex vivo changes in intact human arteries from children with CKD



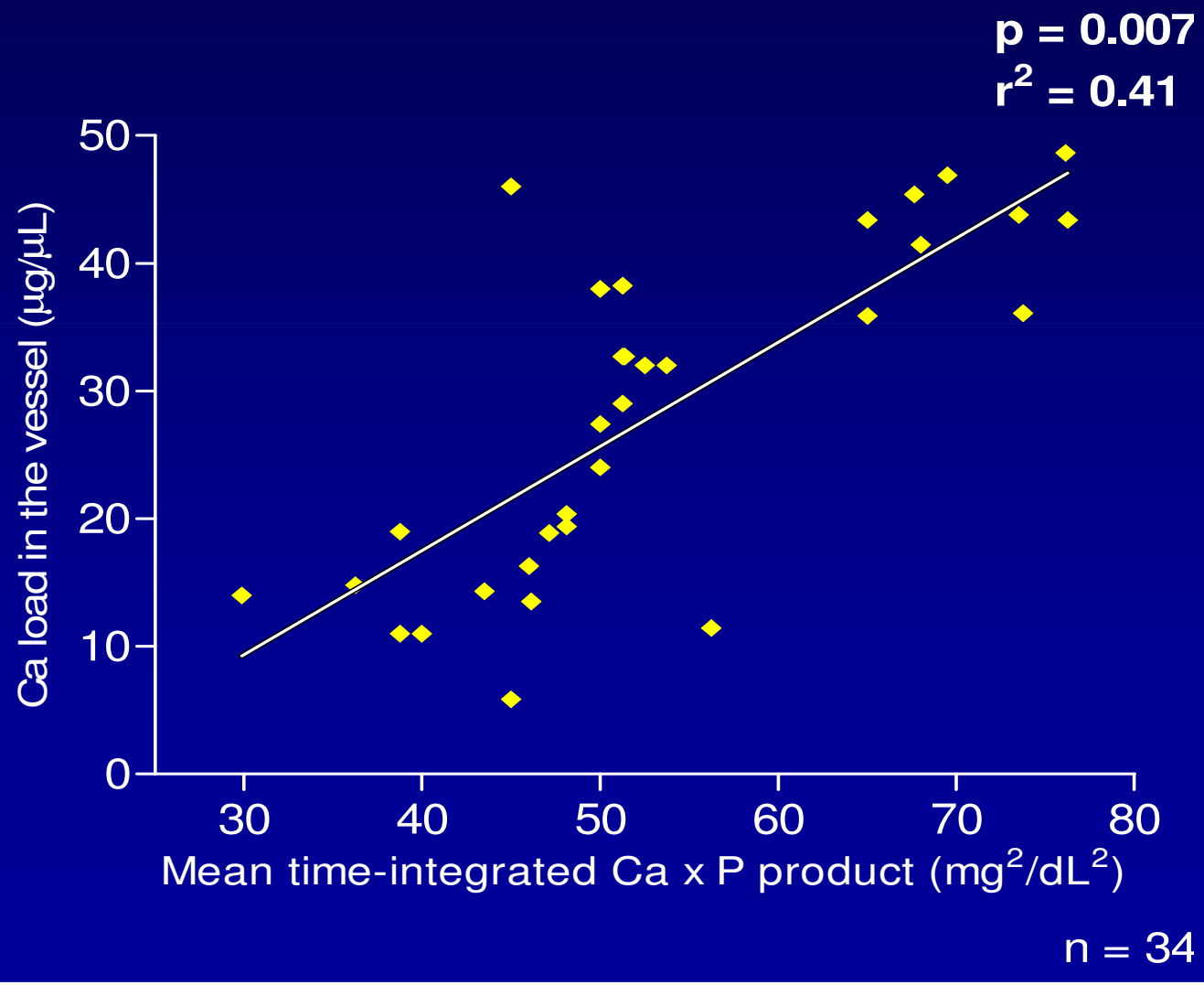


Ca accumulation begins pre-dialysis

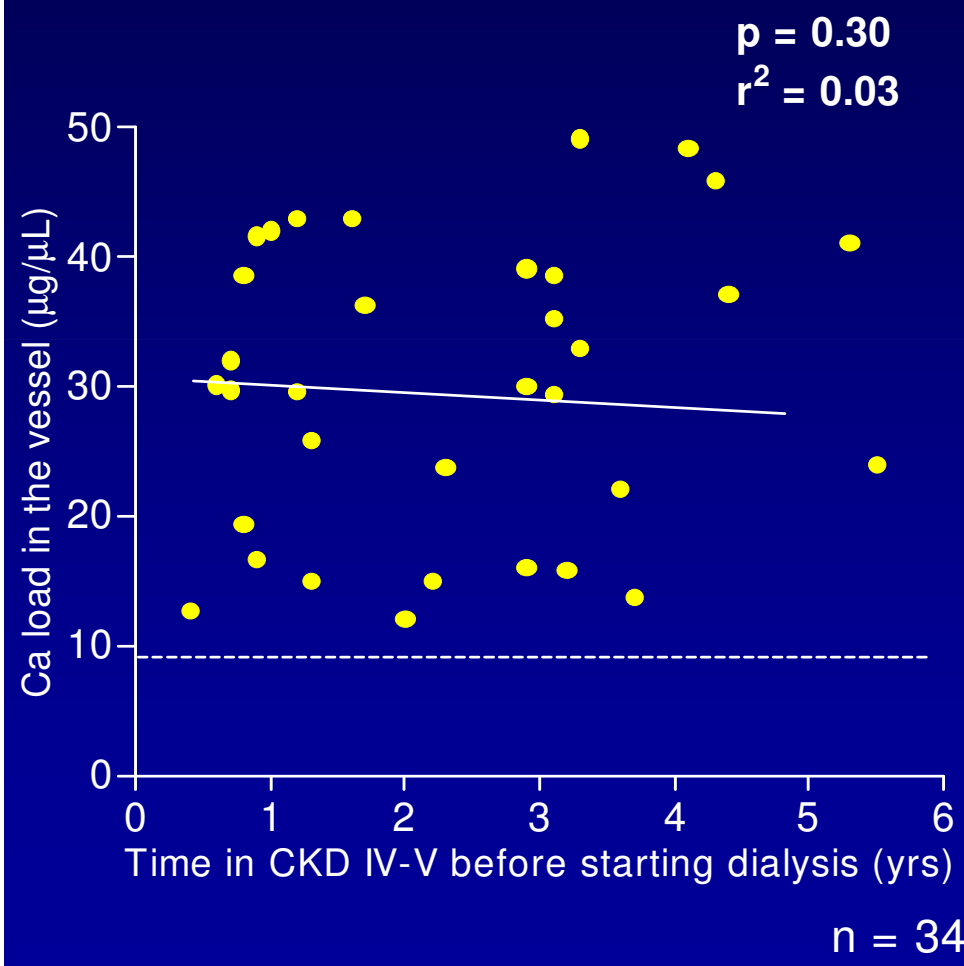


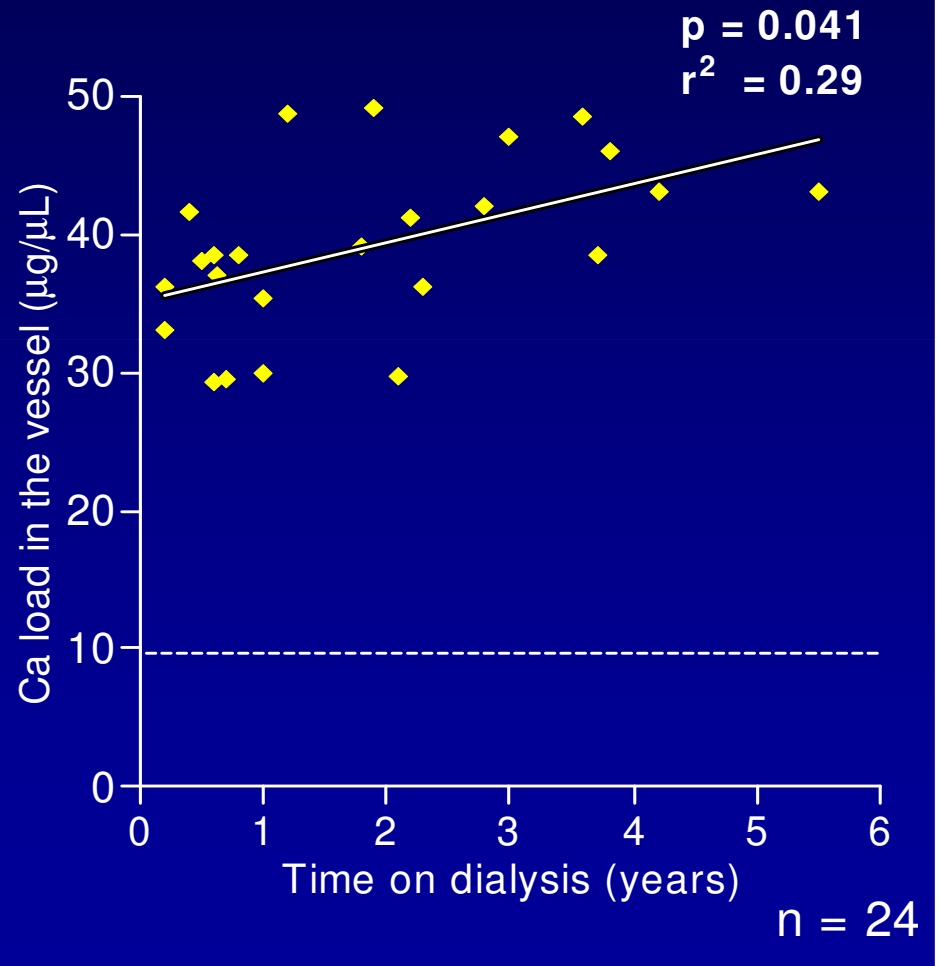


The vessel Ca load correlates with the serum Ca x P product

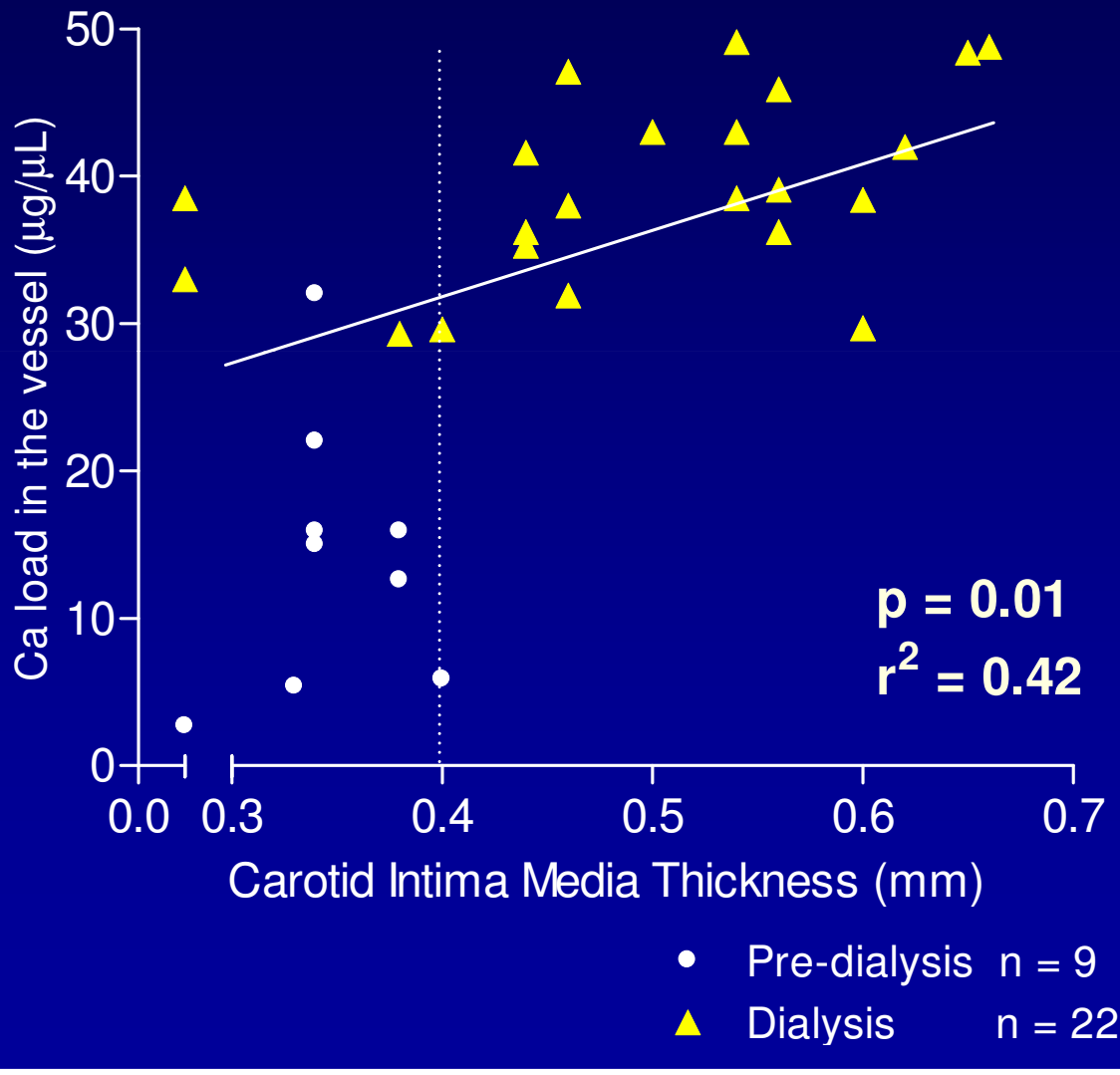


The vessel Ca load increases only with time on dialysis





Ca load correlates with the carotid IMT in dialysis patients



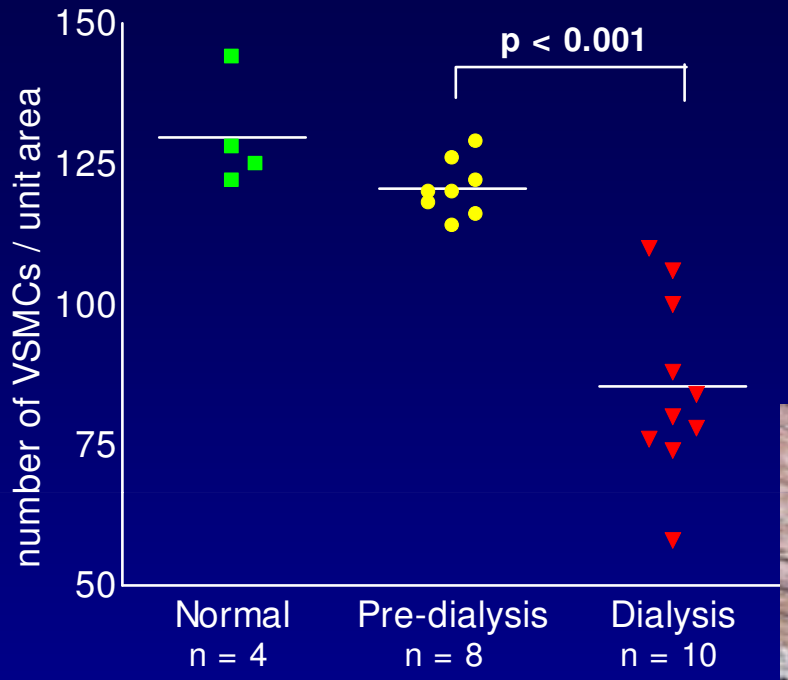
Pulse wave velocity

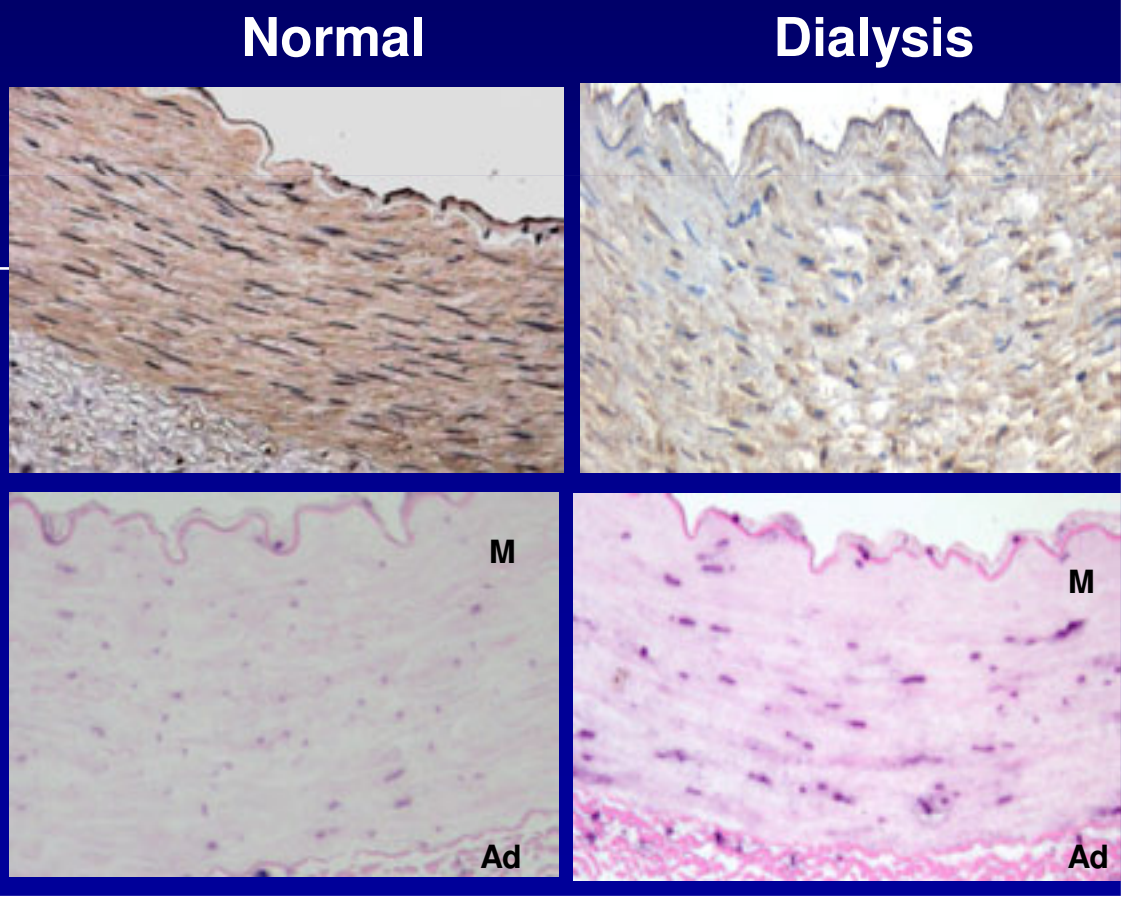
In 2 /31 patients

Coronary calcification on CT scan

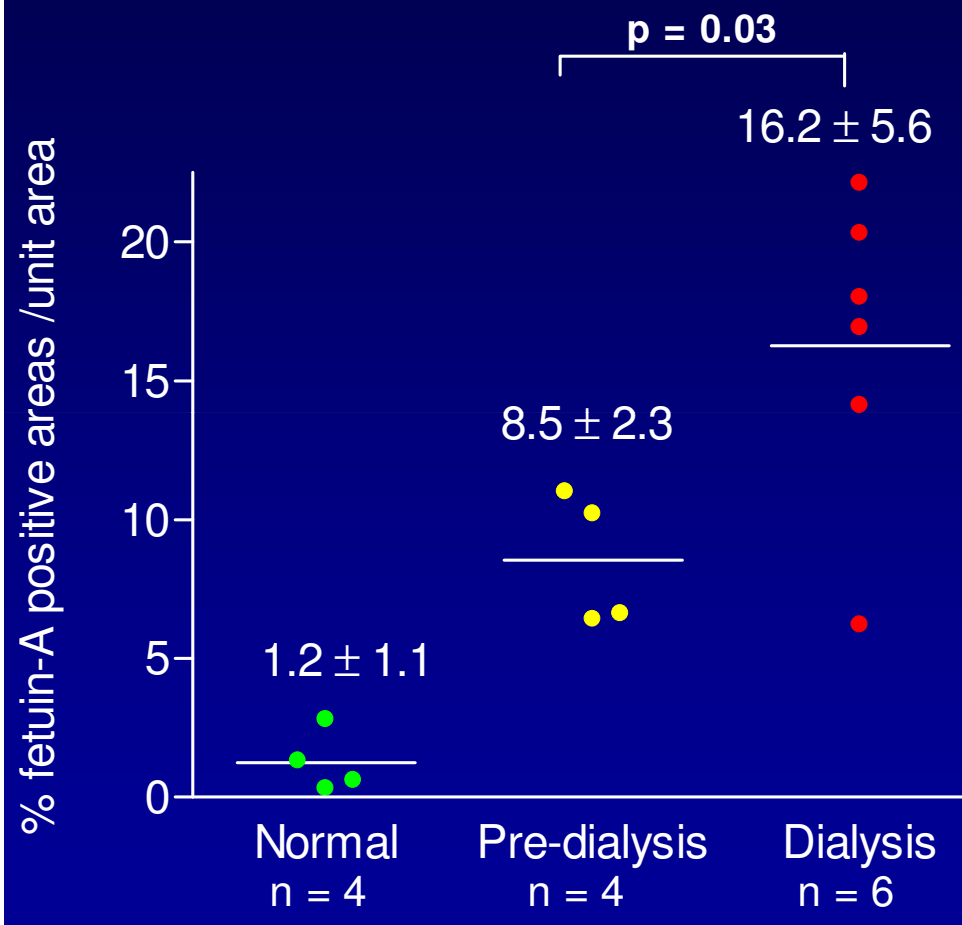
In 2 /31 patients

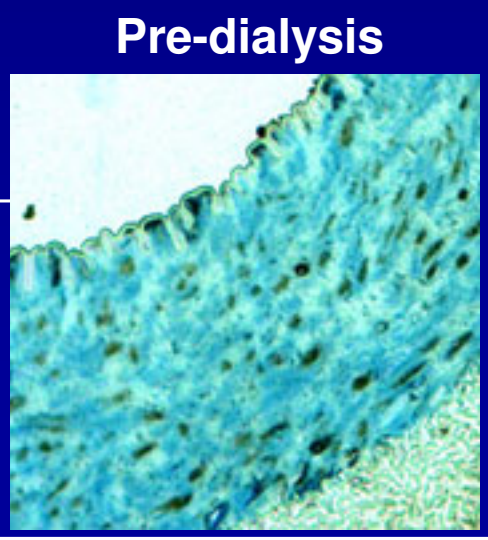
Dialysis vessels have VSMC loss

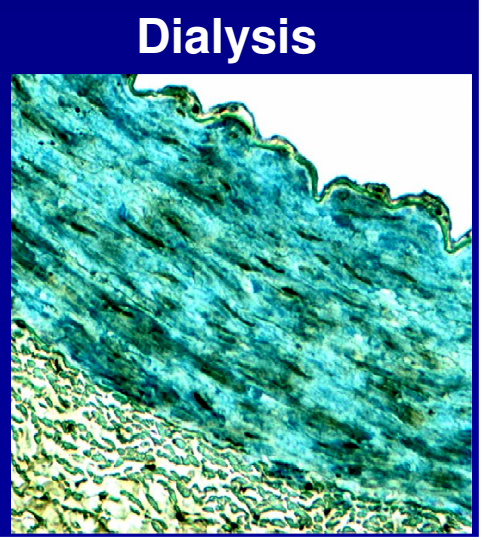




Dialysis vessels have maximum fetuin-A deposition

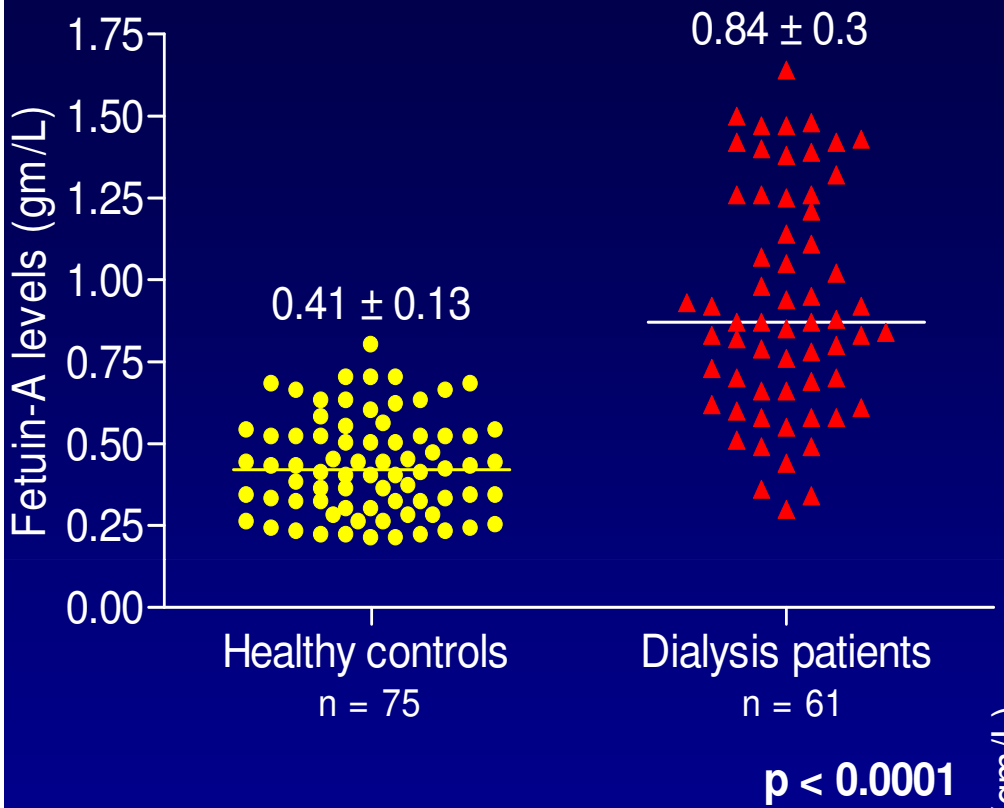


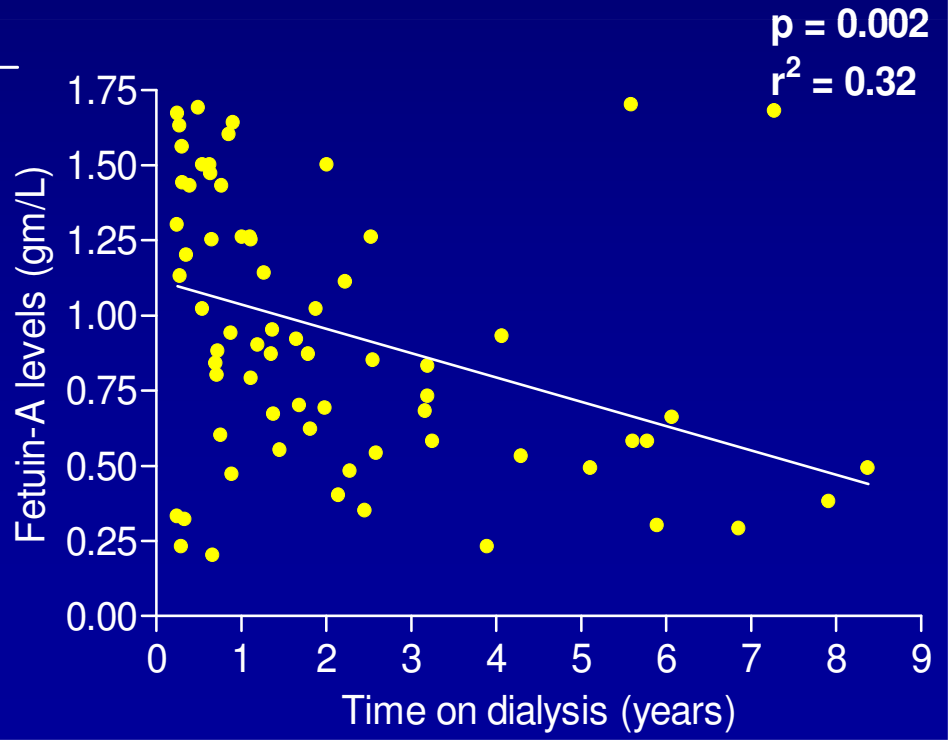




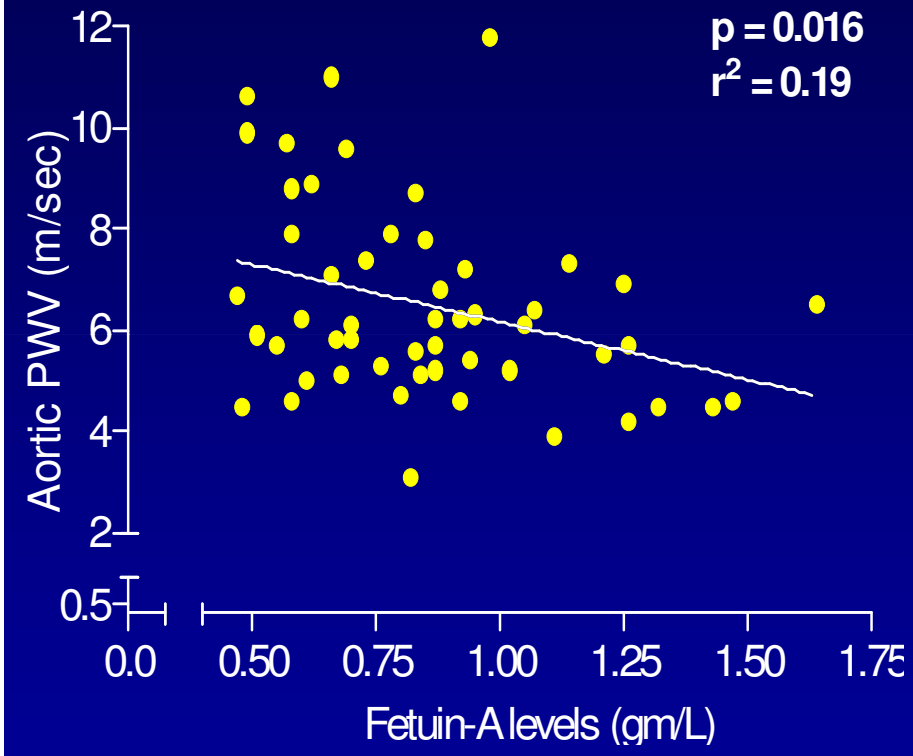
Circulating calcification inhibitors as biomarkers of cardiovascular damage?

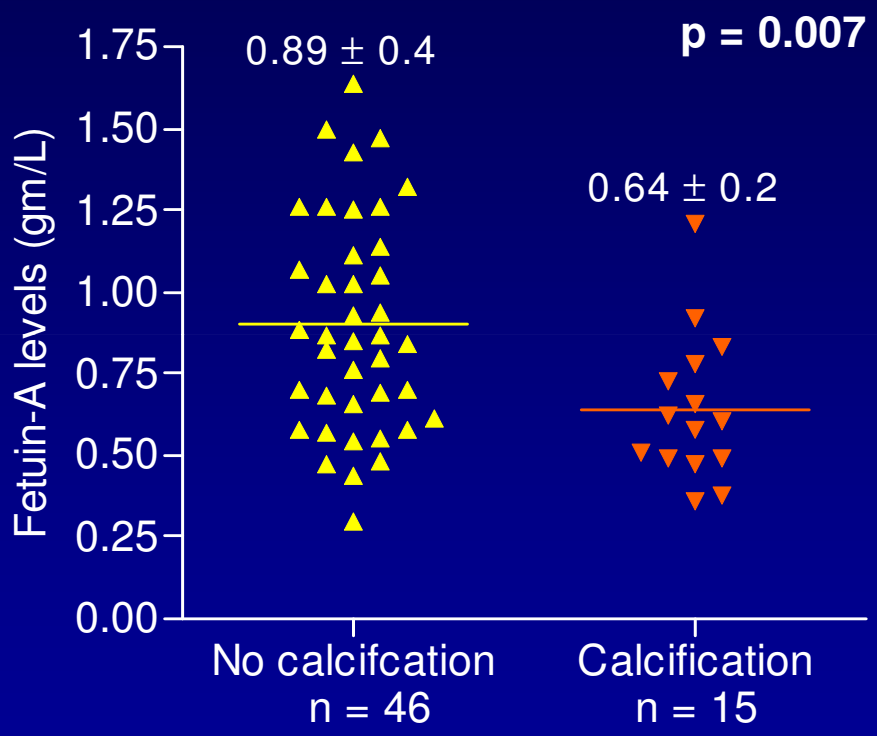
Fetuin-A decreases with time on dialysis





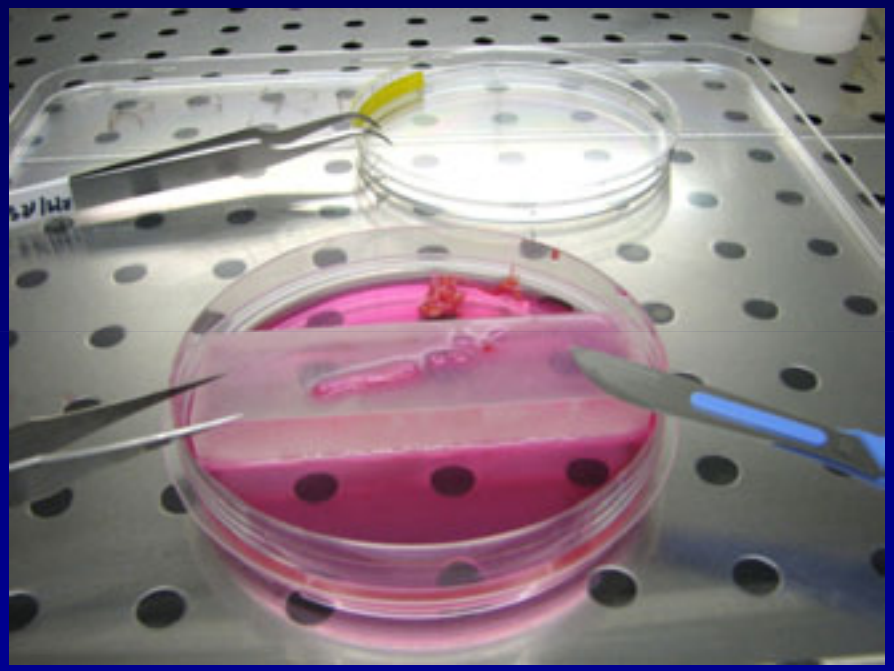
Fetuin levels influence vessel stiffness and calcification

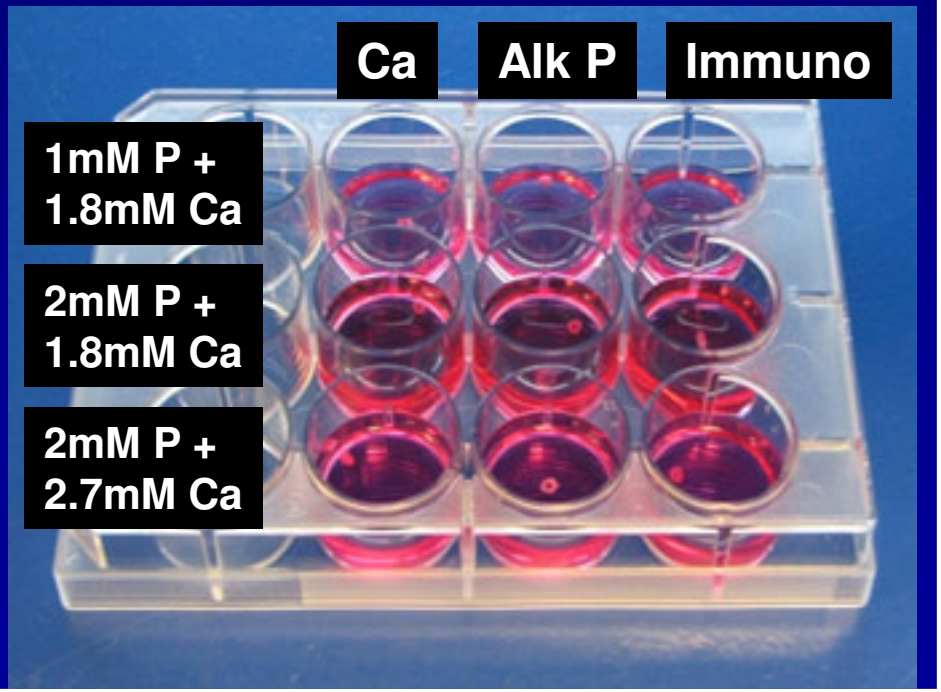




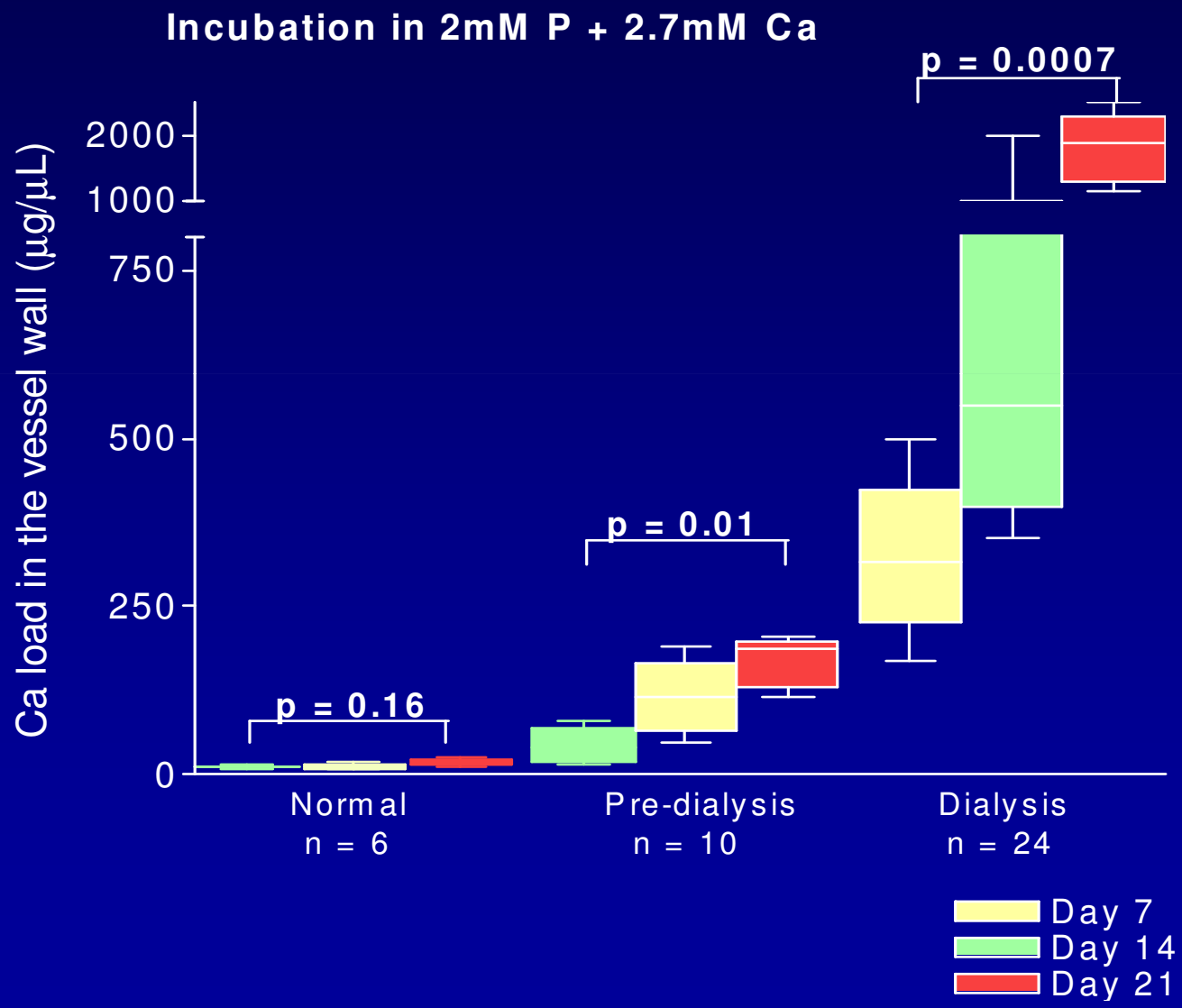
Shroff et al, NDT, 2008

Mechanistic insights into the accelerated calcification in dialysis patients – role of Ca and P

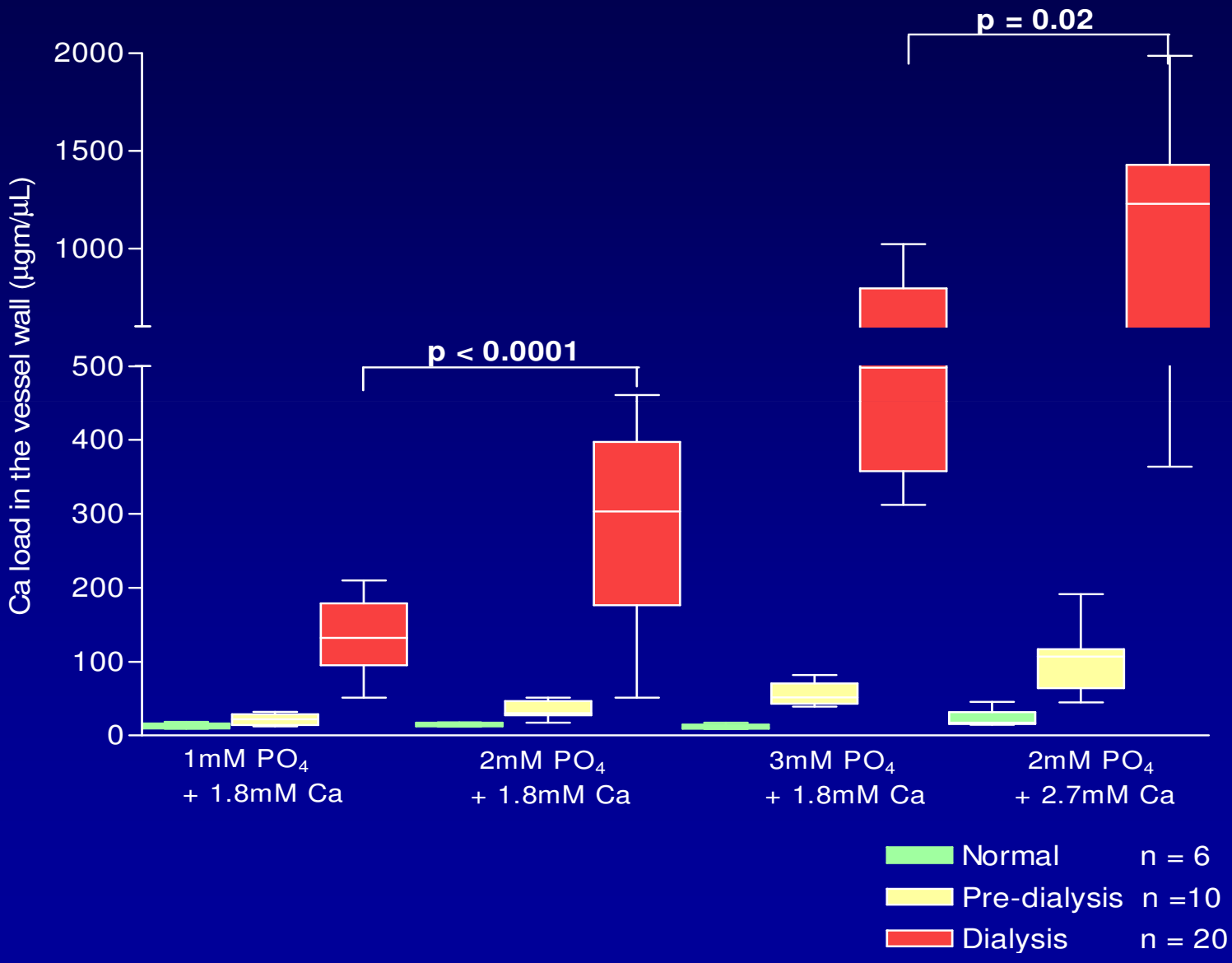


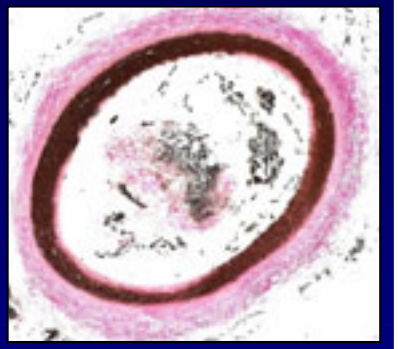


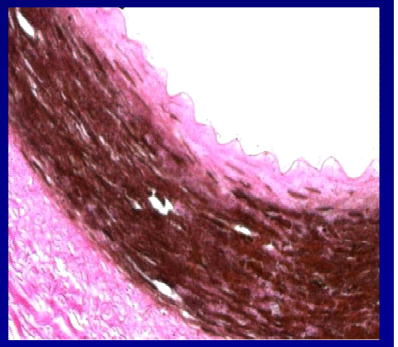
Dialysis vessels have time - dependent Ca accumulation



Ca is more potent at inducing calcification than P

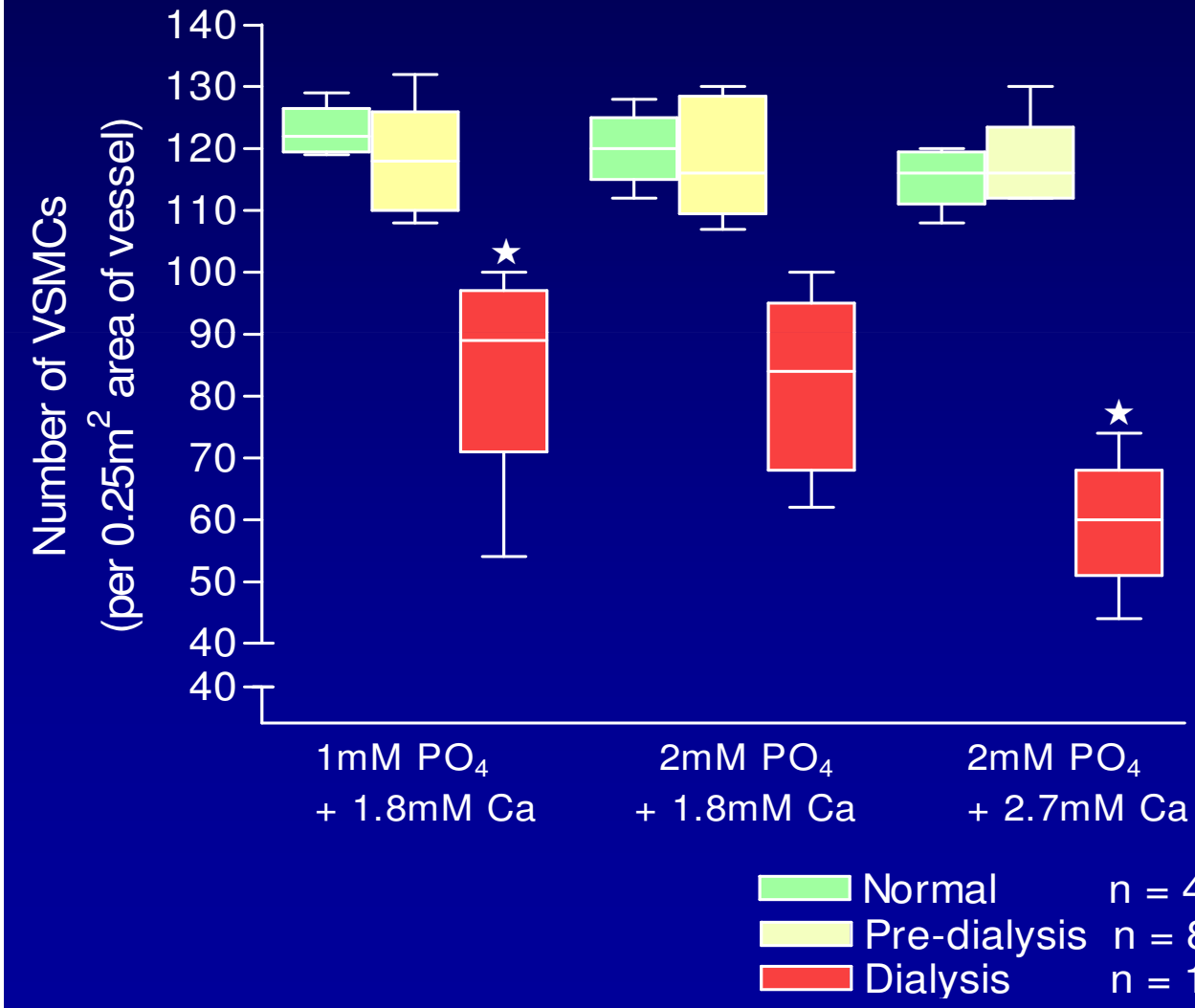




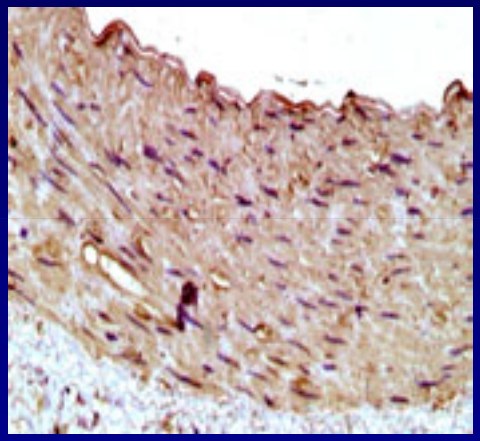


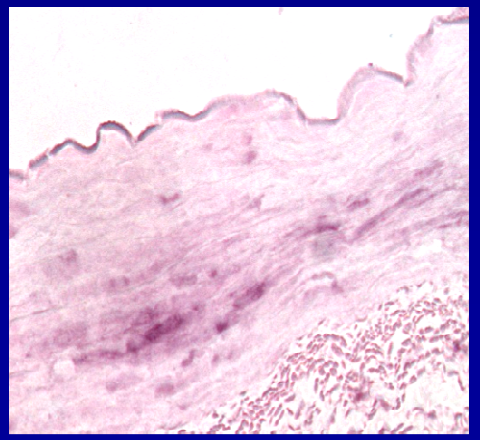
Dialysis vessels have VSMC loss in high Ca + P media

★ p = 0.03

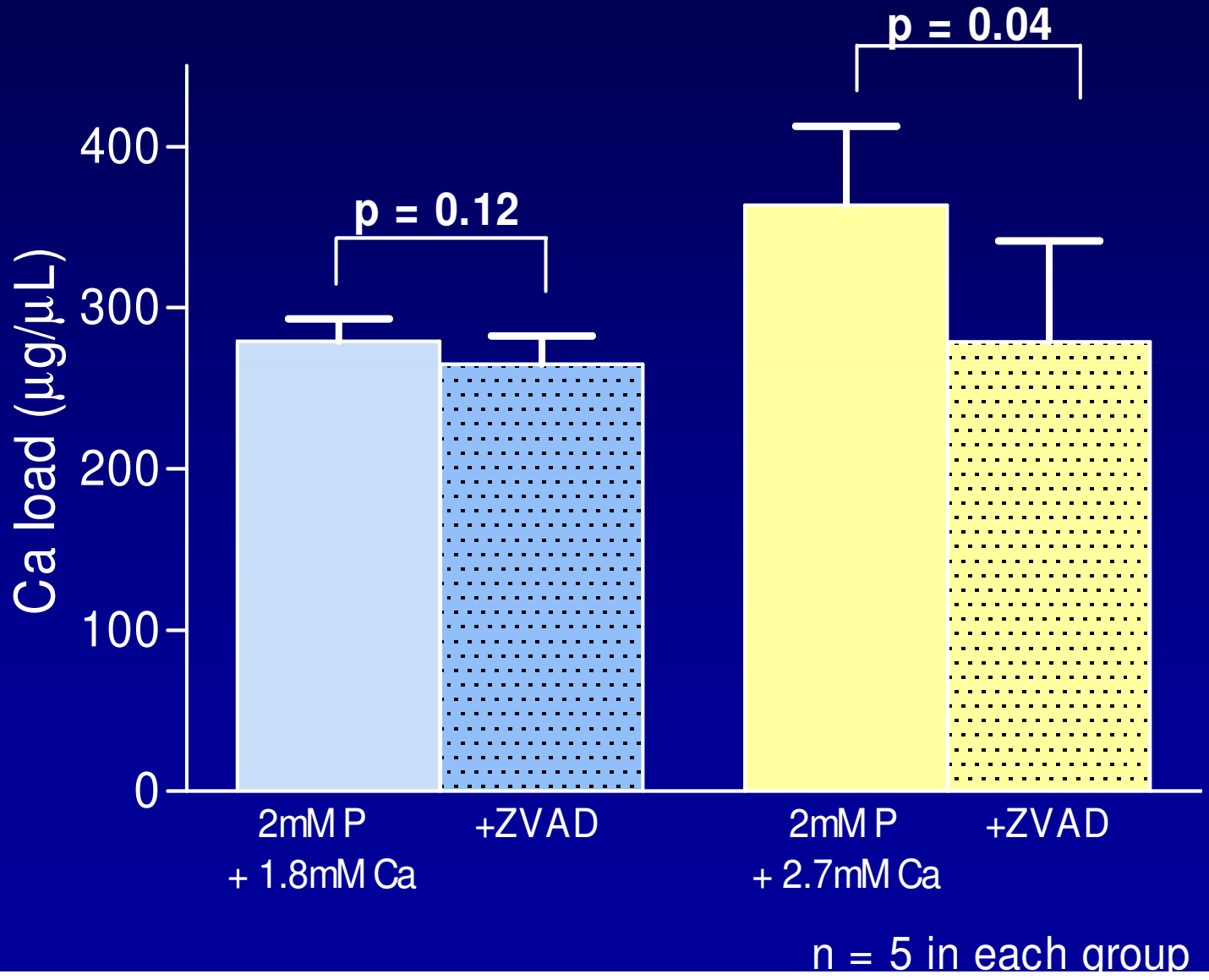


Dialysis – high Ca + P





Ca induced apoptosis may be a prerequisite to calcification



Clinico – pathological correlations

- Ca accumulation begins pre-dialysis and is accelerated on dialysis
- Dialysis vessels have lost protective mechanisms and appear to be ‘primed’ to calcify in high Ca and P conditions
- In the presence of a high P even a small increase in Ca can significantly increase calcification

Progression of vasculopathy

Conclusions

- Calcification begins early in CKD and progresses inexorably on dialysis
- Transplantation can only partially reverse the effects of dialysis on the vasculature
- Our currently available imaging techniques are not sensitive enough to detect early vascular calcification

Prevention is key

- **Prevent mineral dysregulation**
- **Maintain normal vit D levels**
- **Pre-emptive renal transplantation**

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