# CKD-MBD in children



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# Disclosures

*Speaker:* Gambro, Baxter, Genzyme, Amgen

*Educational / Research support:* Gambro

# Children are not small adults

- Children have higher Ca and P requirements
- Total skeletal Ca increases from ~25g at birth to ~1000g in an adult
- Buffering capacity of the growing skeleton



| Age, years | Calcium threshold (mg/day) | Balance per day (mg/day) |
|---|---|---|
| 0-1 | 1090 | 503±91 |
| 2-8 | 1390 | 246±126 |

**Calcium balance is positive throughout childhood**

# Paediatric CKD-MBD studies

- No RCTs
  - Registry reports
  - Longitudinal studies in pre-dialysis and dialysis
- No ‘hard’ end-points for vascular studies
  - Surrogate measures of vascular disease
  - *Ex vivo* changes in vessels



‘Clean population’

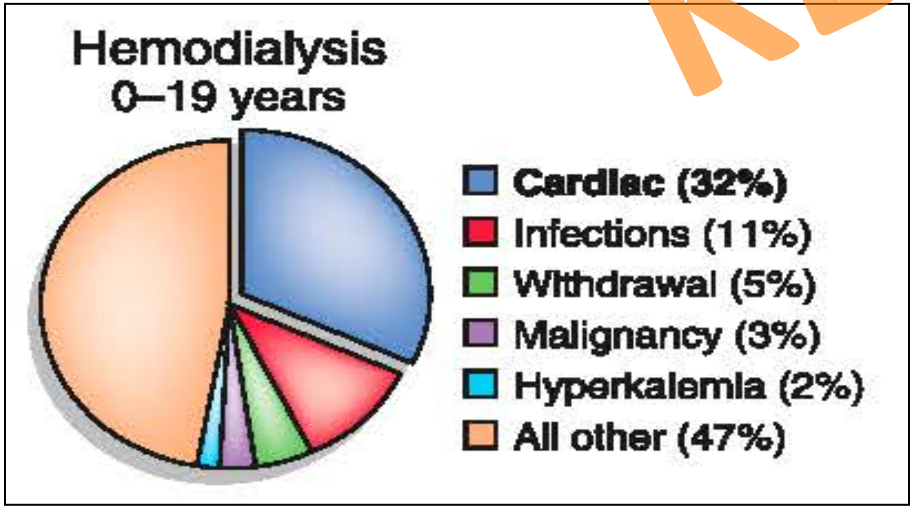
- no pre-existing CVD
- rarely have diabetes or underlying inflammatory disease
- some studies have selected children without uncontrolled HT or dyslipidaemia

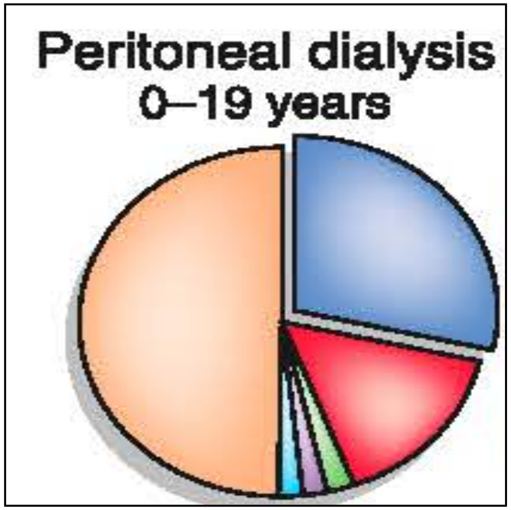
# Outline

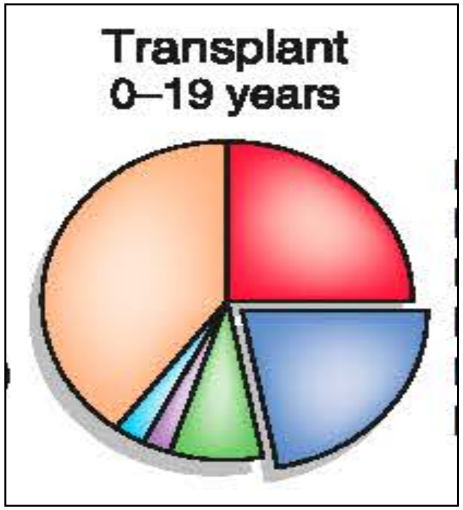
- CKD-MBD evolution in children
- Paediatric CVD and MBD
  - single / multicentre studies
  - Registry reports
  - Longitudinal studies on progression of vascular and bone disease
- Vessel and bone biopsy data

# CKD-MBD in children






*USRDS 2011 report*

# Vascular changes begin pre-dialysis

Chronic Kidney Disease in Children

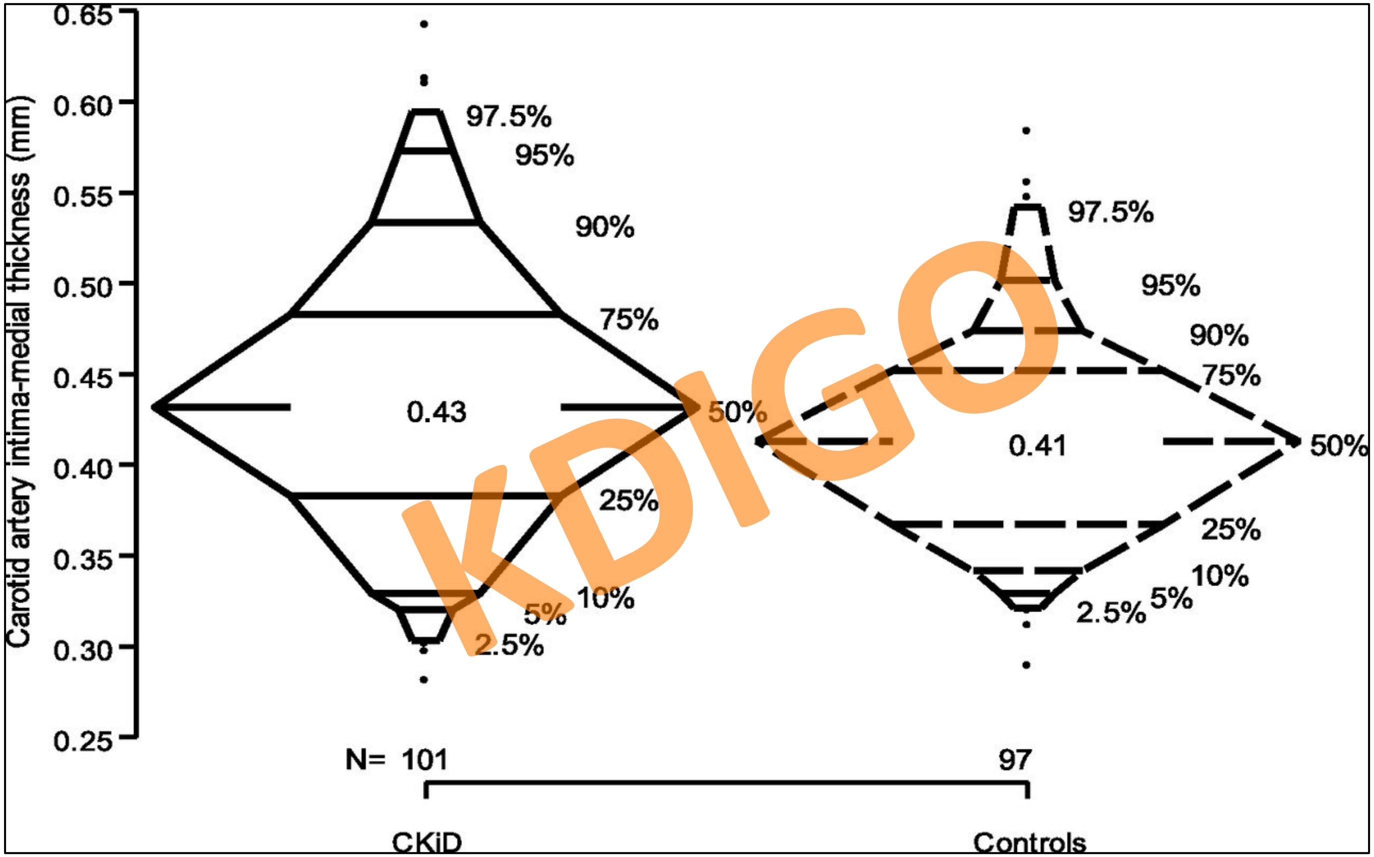
586 children; age 1-16 years
eGFR 30-90 mL/min/1.73 $m^2$



CC CC Cardiovascular comorbidity in childhood CKD

700 children; age 6 – 18 years
eGFR 10 – 45ml/min/1.73$m^2$

# Increased cIMT in pre-dialysis CKD

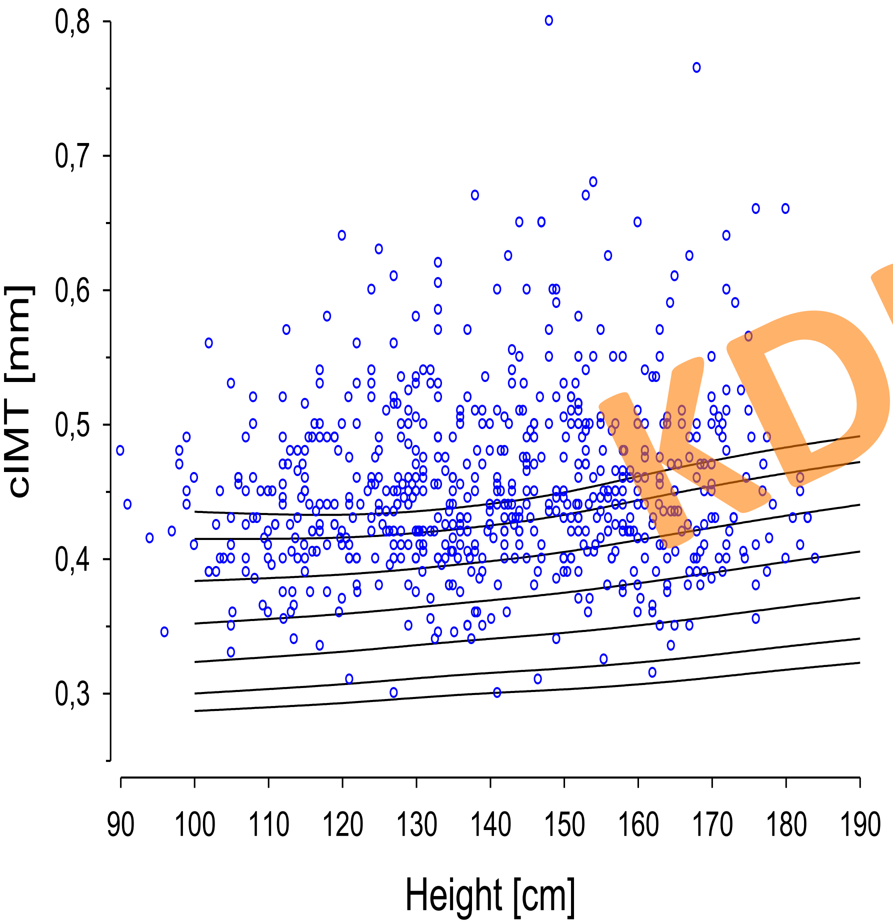



- 100 children with a median GFR 43 ml/min/1.73 $m^2$
- Increased cIMT was associated with HT and dyslipidemia

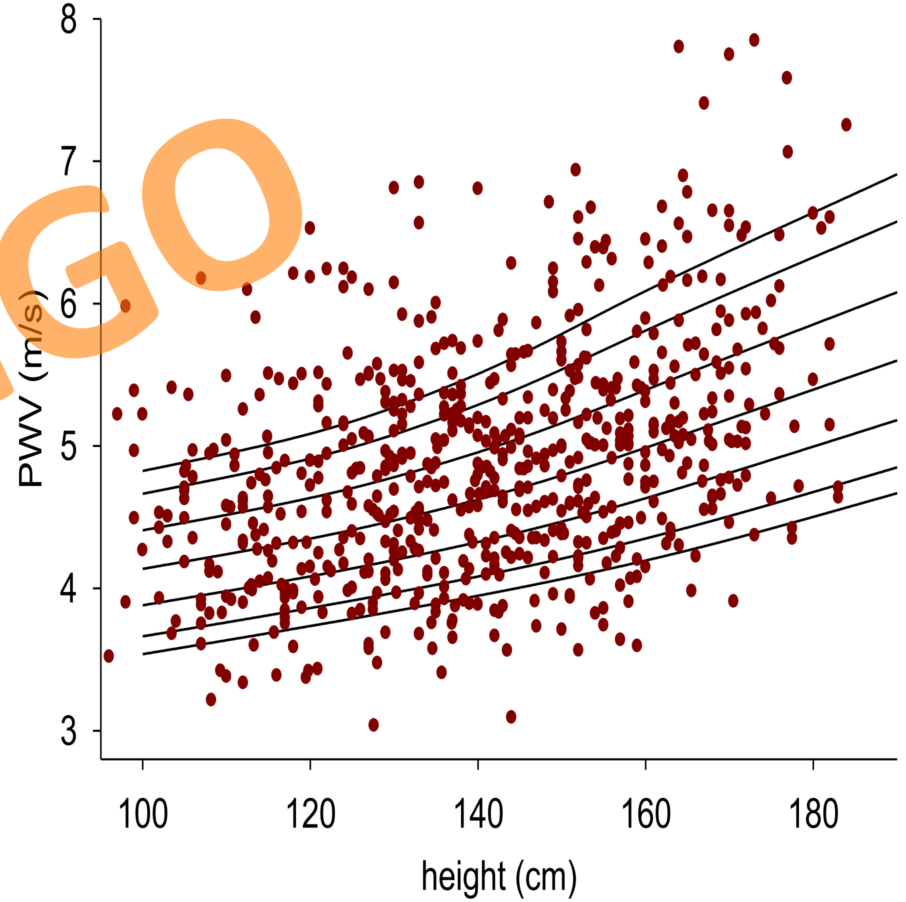
*Brady et al; CJASN 2012*

# Increased cIMT & PWV pre-dialysis

## Intima Media Thickness




## Pulse Wave Velocity






N = 700
eGFR 10 – 45ml/min/1.73m²

*Slide courtesy of Prof Schaefer*

# Predictors of cIMT and PWV

## IMT SDS

| | Beta | Partial $R^2$ | Model $R^2$ | p |
|---|---|---|---|---|
| **Systolic BP SDS** | 0.17 | 0.029 | 0.029 | 0.0005 |
| **S-Phosphate** | 0.55 | 0.028 | 0.056 | 0.0005 |
| **S-Calcium** | -1.03 | 0.022 | 0.078 | 0.0016 |
| **25OH Vitamin D** | -0.02 | 0.014 | 0.092 | 0.012 |



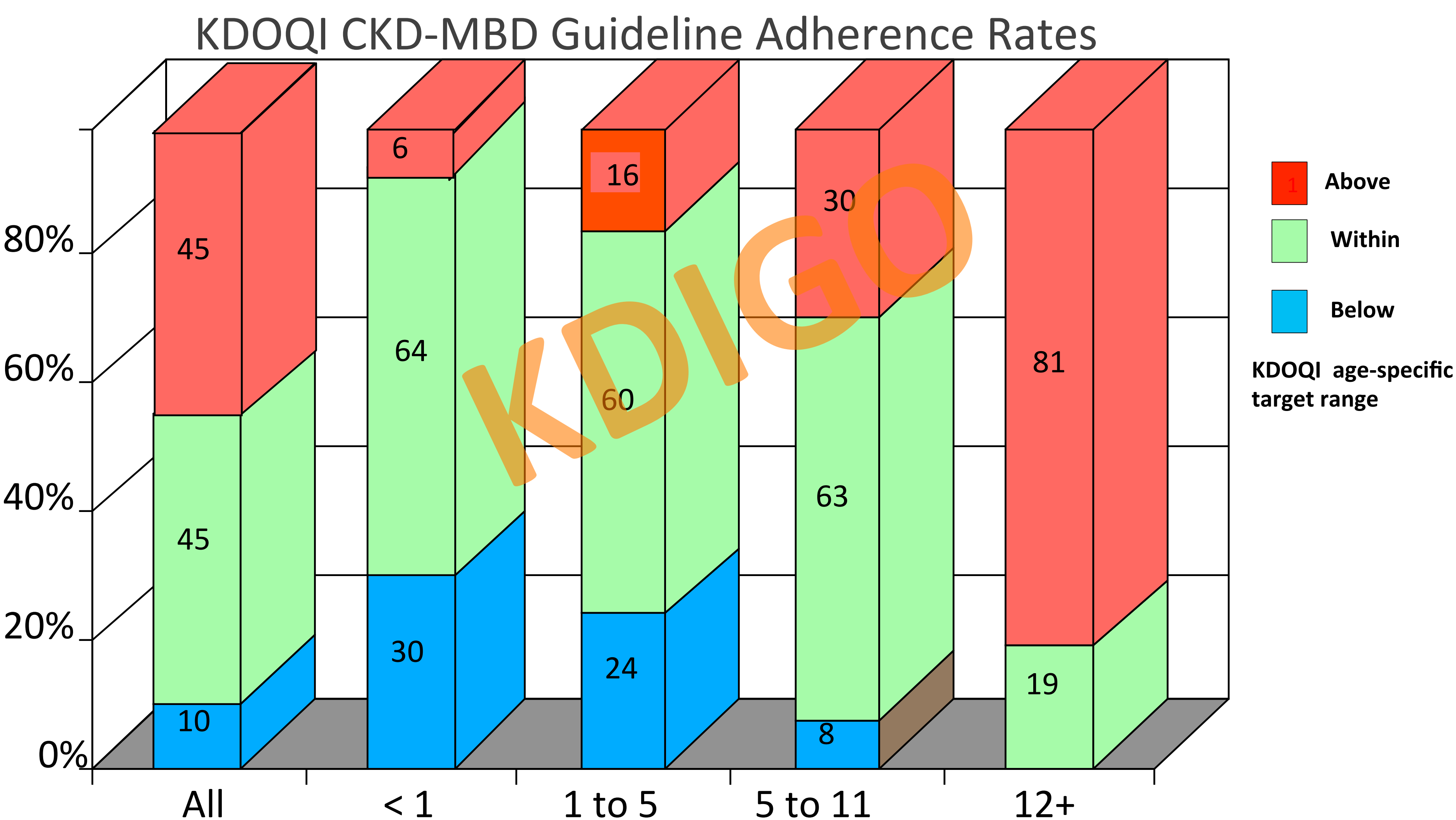
## PWV SDS

| | | | | |
|---|---|---|---|---|
| **Systolic BP SDS** | 0.42 | 0.126 | 0.126 | <.0001 |
| **25OH Vitamin D** | -0.025 | 0.032 | 0.158 | 0.0002 |
| **S-Phosphate** | 0.52 | 0.014 | 0.171 | 0.0115 |
| **iPTH** | 0.006 | 0.007 | 0.179 | 0.0675 |

*Slide courtesy of Prof Schaefer*

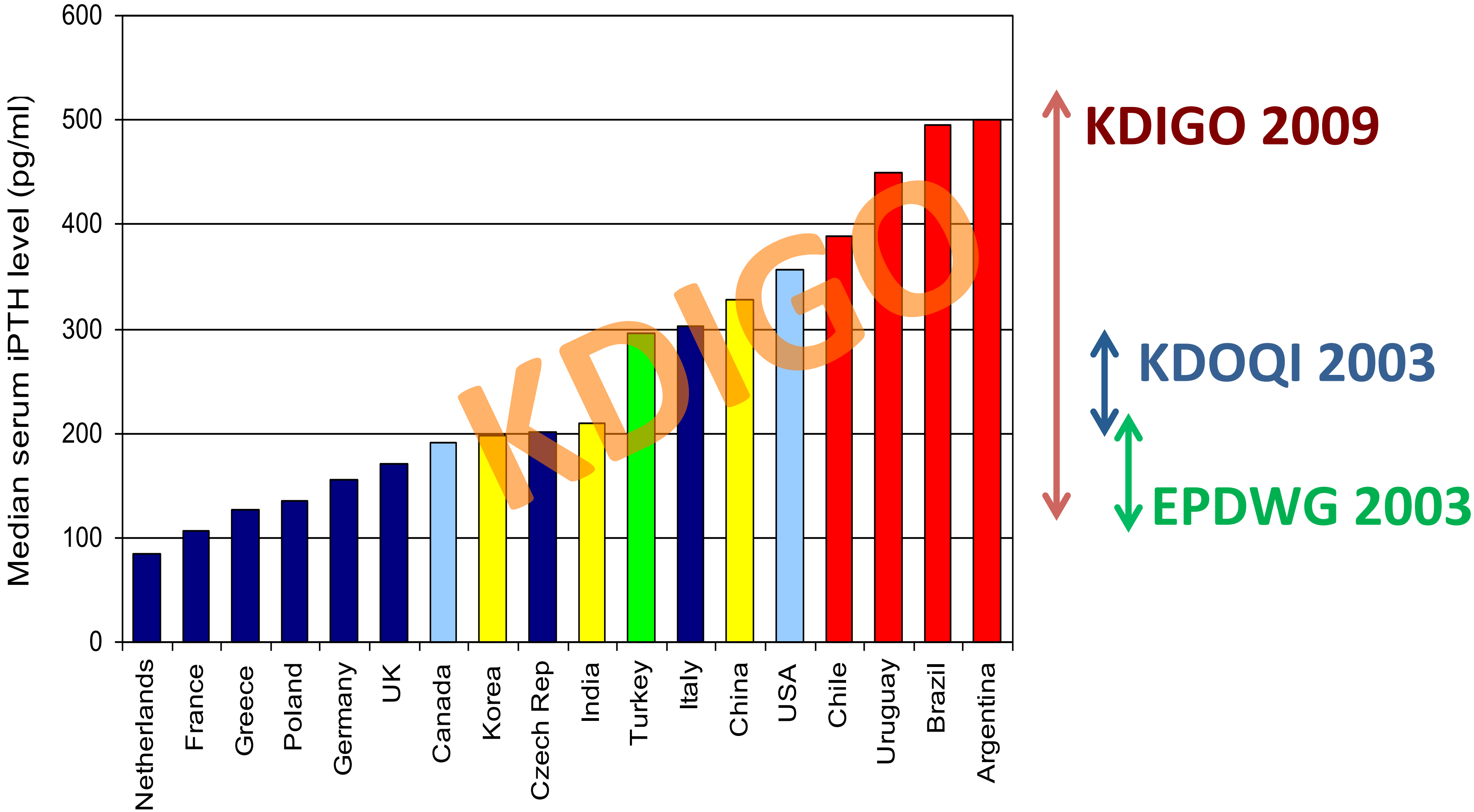
# Studies in dialysis patients

# High P levels in 45% of PD patients




International Pediatric Peritoneal Dialysis Network

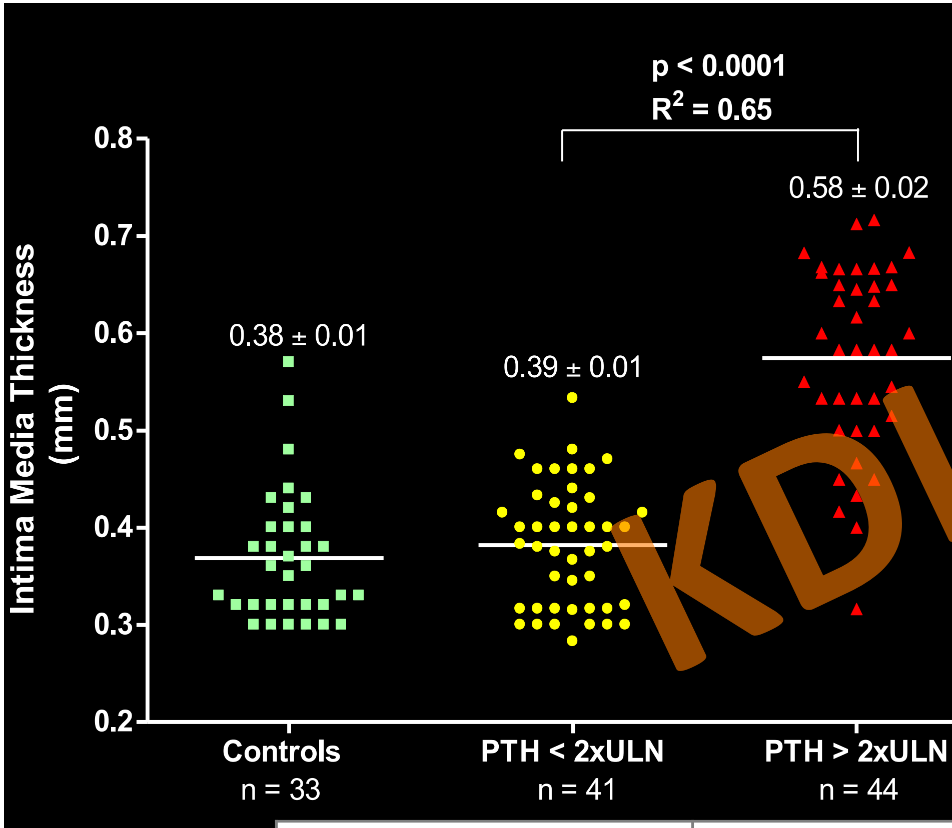
# PTH levels in PD patients

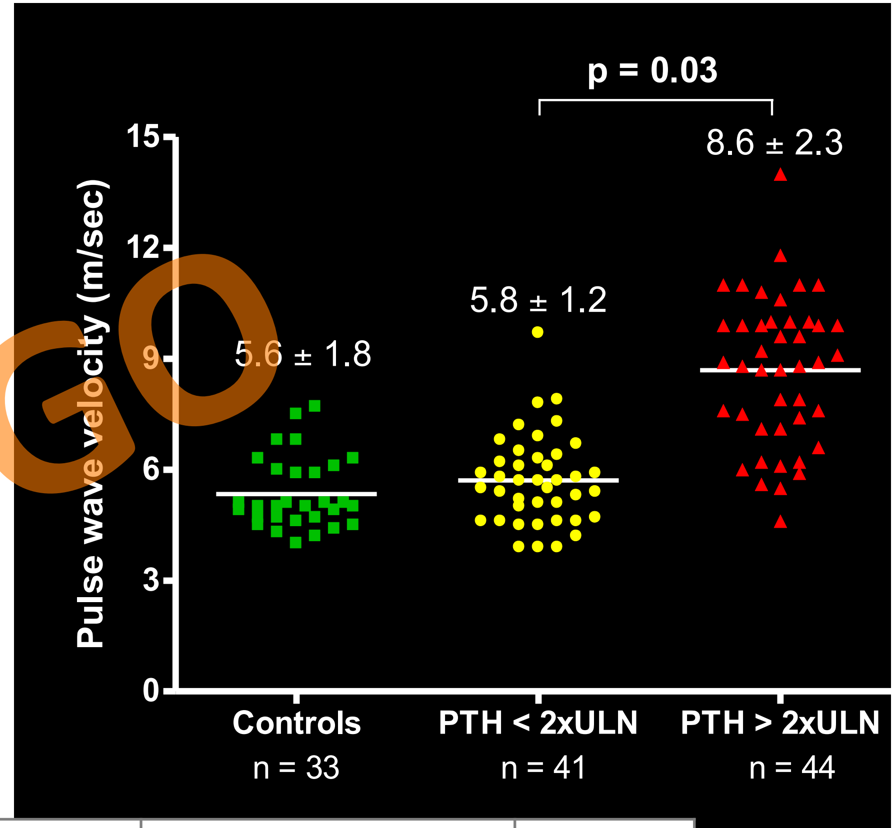



International Pediatric Peritoneal Dialysis Network

| Authors / Journal | Number of dialysis pts | Vascular measures | Clinical / biochemical associations with cIMT |
|---|---|---|---|
| Oh / Circulation 2002 | 39 | cIMT<br>CAC | - dialysis duration<br>- mean serum P<br>- PTH levels |
| Litwin / JASN 2005 | 37 | cIMT | - dialysis duration<br>- mean serum P<br>- Mean calcitriol dose |
| Mitsnefes / JASN 2005 | 16 | cIMT<br>distensibility | - dialysis duration<br>- mean serum Ca x P<br>- Mean calcitriol dose<br>- mean PTH levels |
| Shroff / JASN 2007 | 85 | cIMT<br>PWV<br>CAC | - dialysis duration<br>- mean serum P and Ca x P<br>- Mean calcitriol dose<br>- mean PTH levels |
| Civilibal / Ped Neph 2007 | 37 | cIMT<br>FMD<br>ECHO | - mean serum P<br>- total & LDL cholesterol<br>- mean calcitriol dose |
| Reusz / Ped Neph 2009 | 11 | PWV | - mean serum Ca x P<br>- mean calcitriol dose |

# PTH is associated with calcification



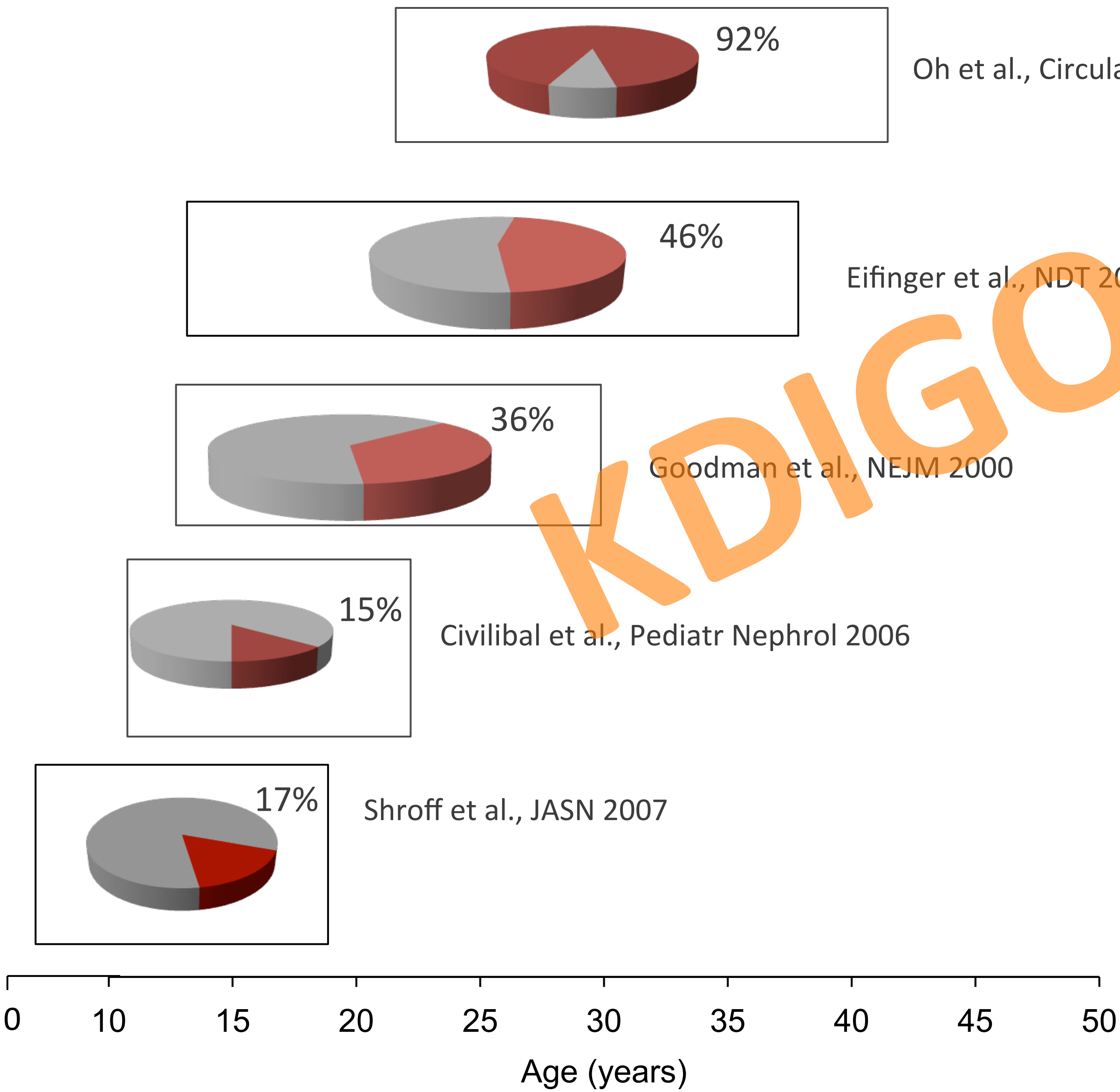






| | PTH <2 ULN n = 41 | PTH >2 ULN n = 44 | p |
|---|---|---|---|
| **Total** | 5 (12%) | 12 (27%) | <0.01 |
| **Calcification score** | 7.8 (0 – 98) | 85.3 (0 – 2039) | 0.001 |

*N 2007*

# CAC in children and young adults





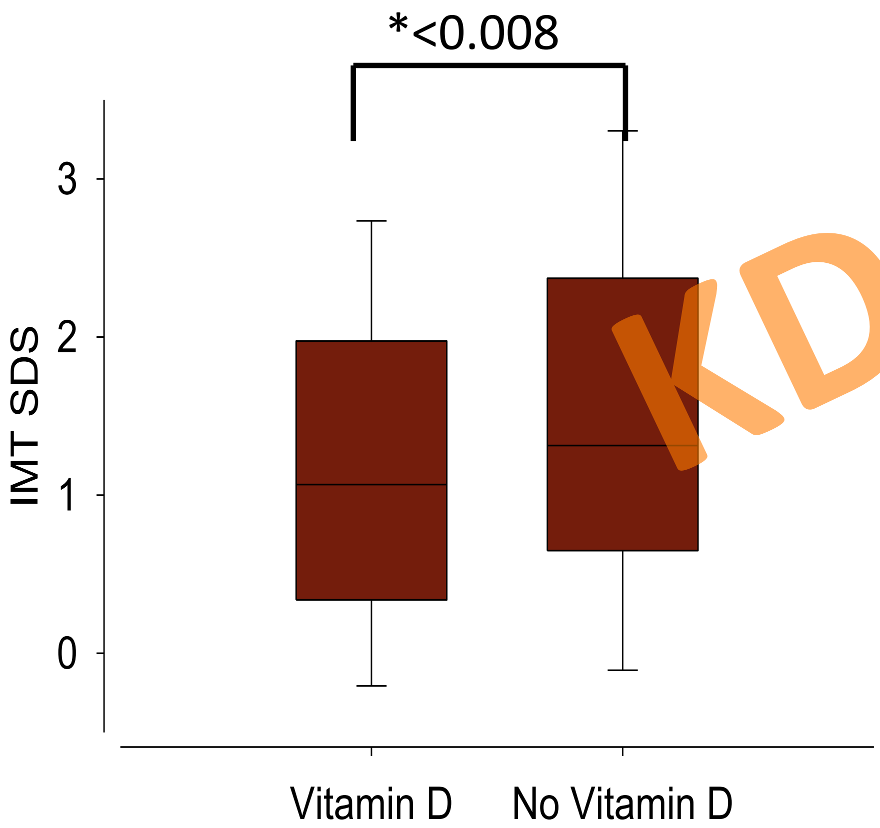

**Predictors of CAC**

- age
- dialysis duration
- serum P
- PTH
- hs-CRP
- Higher Ca intake from binders

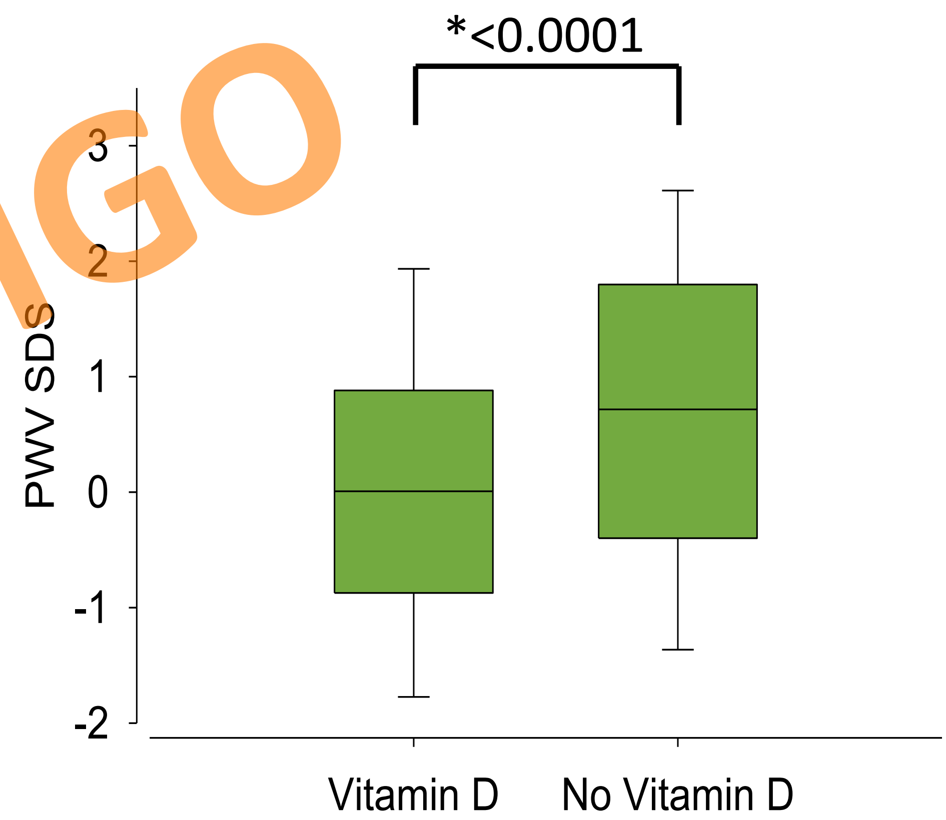
# Effects of vitamin D supplementation

# Vit D supplements (Ergo/ cholecalciferol) in pre-dialysis CKD

## Intima Media Thickness



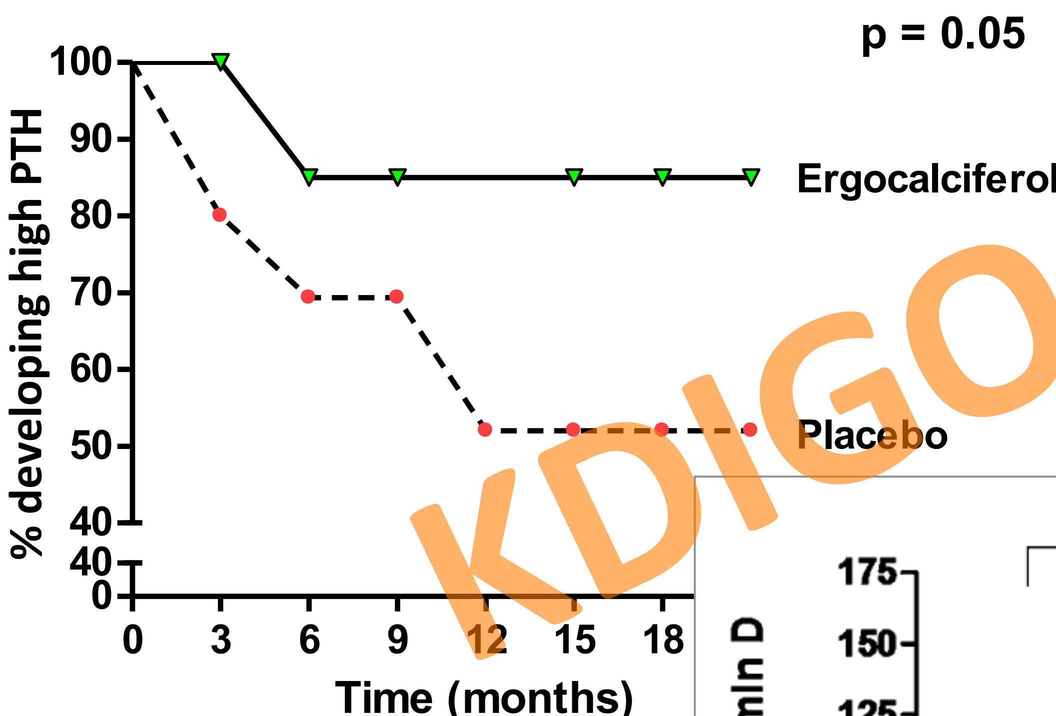

## Pulse Wave Velocity





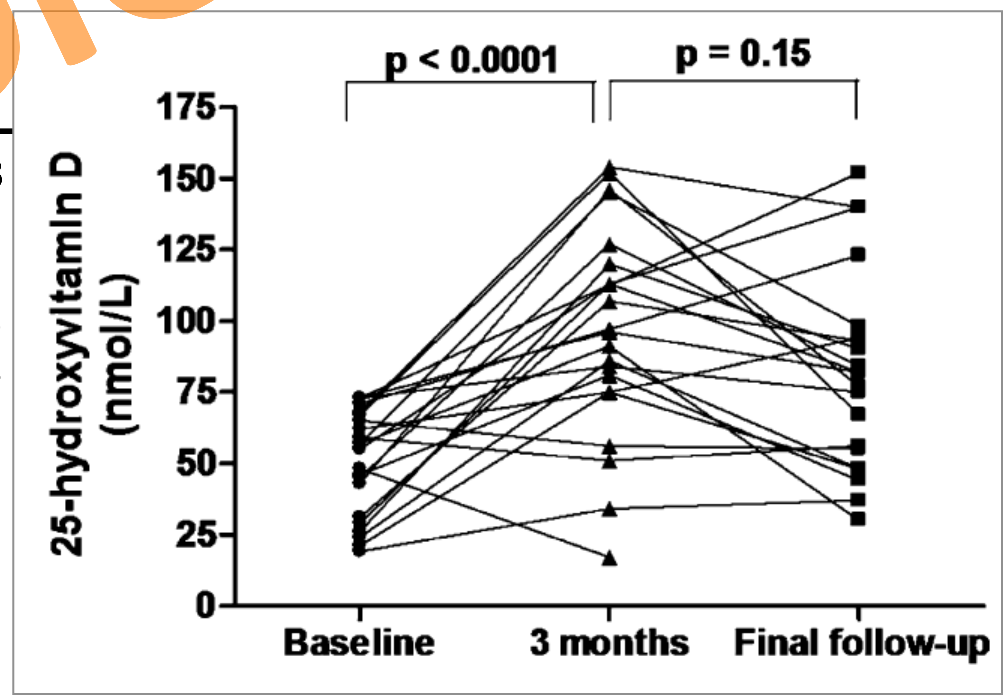

*Slide courtesy of Prof Schaefer*

# Ergocalciferol in CKD2-4 delays the onset of secondary hyperparathyroidism




**Number at risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ergocalciferol | 20 | 20 | 19 | 17 | 16 | 12 | 9 |
| Placebo | 20 | 20 | 15 | 13 | 12 | 8 | 5 |



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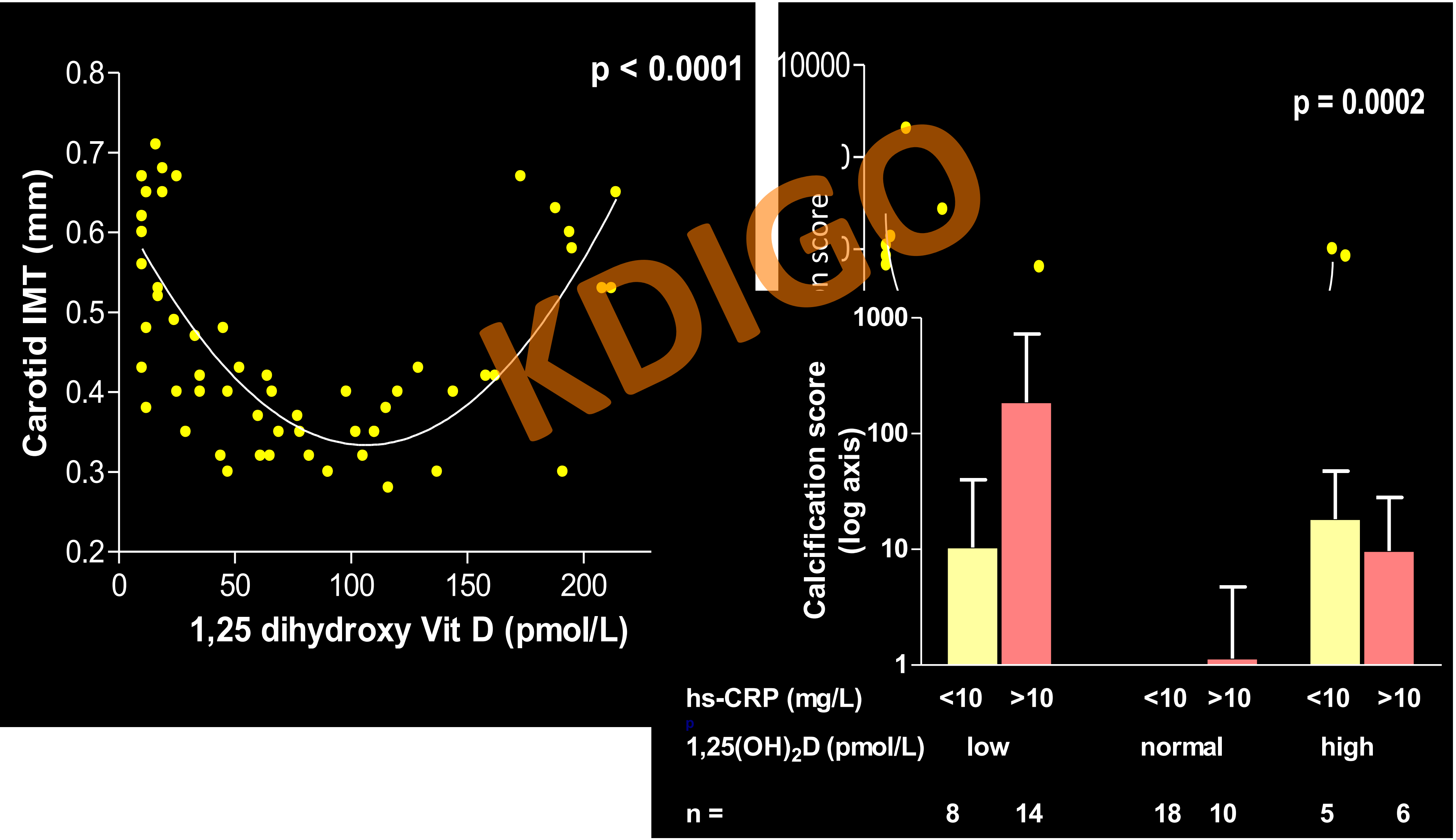
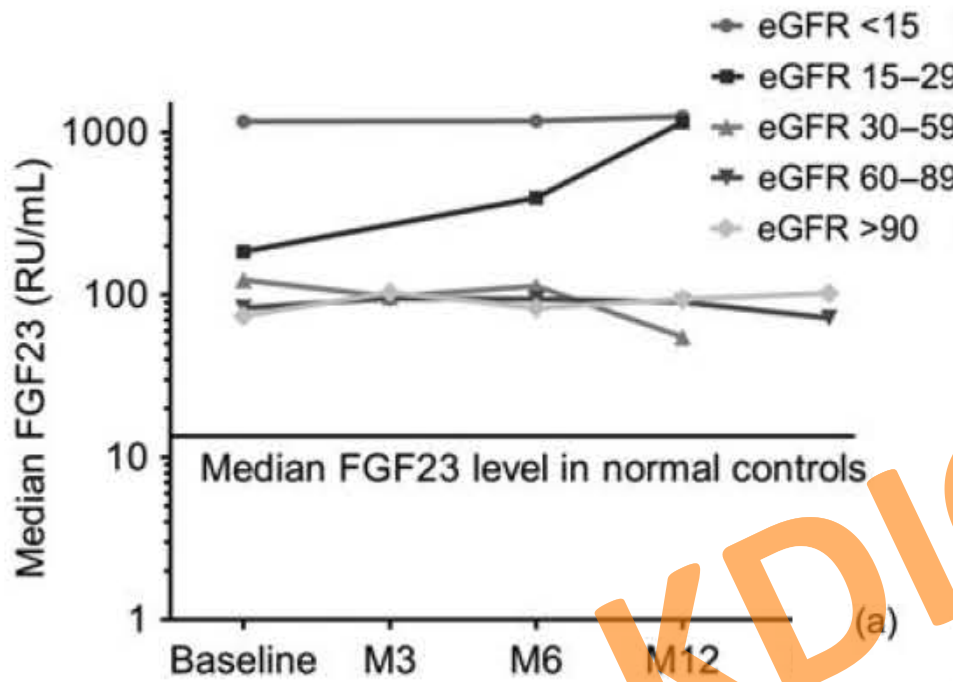
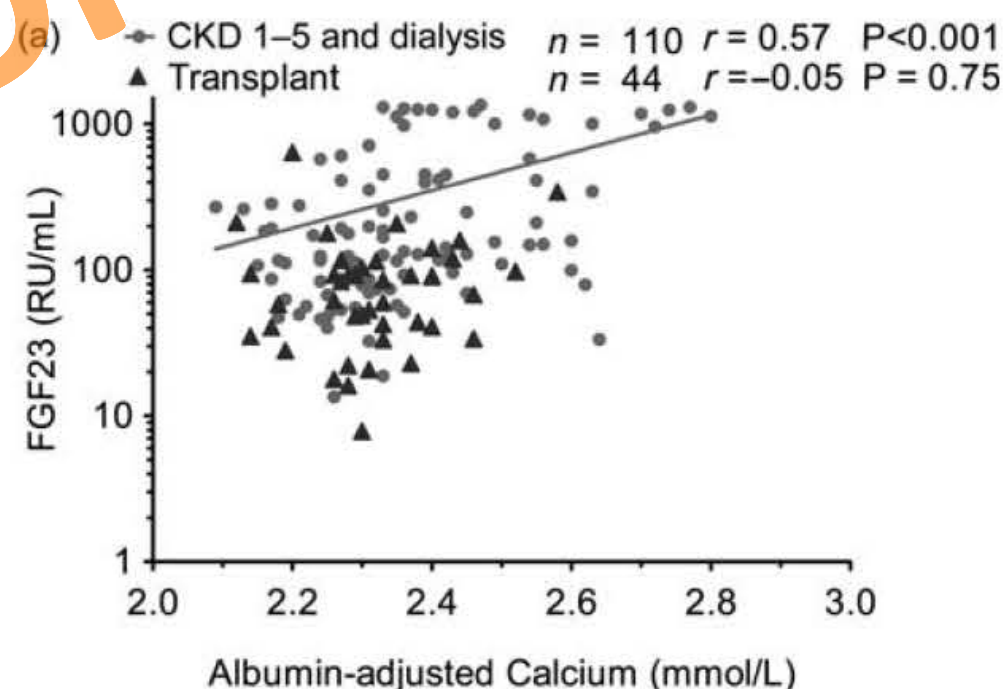
# Bimodal effect of 1,25 dihydroxy D



# Association with FGF23



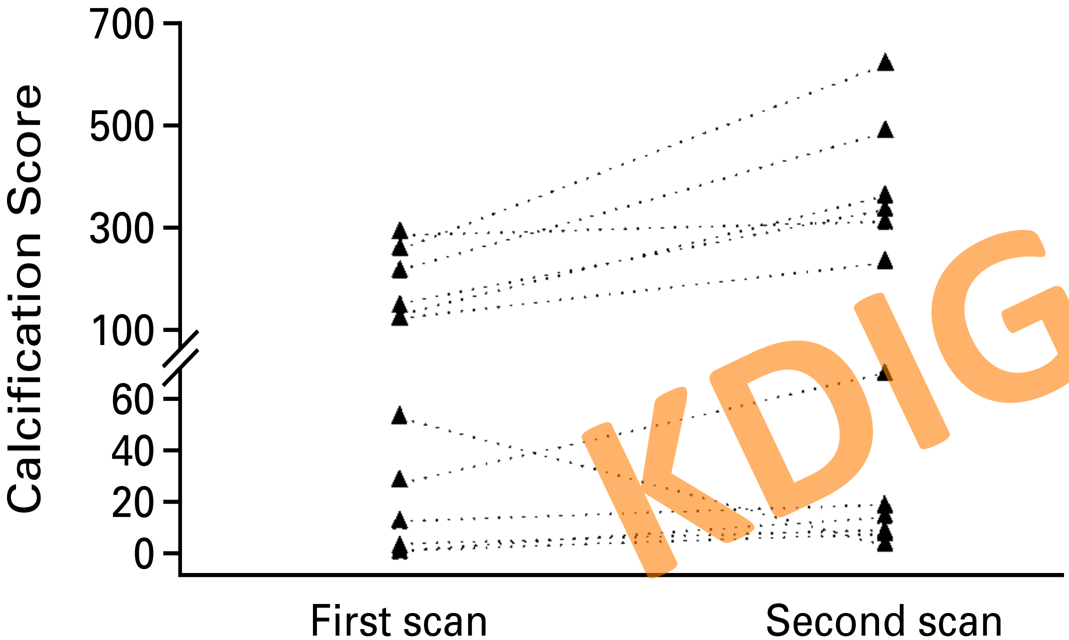






Wan and Shroff; NDT 2012

# Progression of vascular disease

# P levels determine progression of coronary calcification




Serum P positively correlated with doubling of calcification scores within 20 months

*Goodman et al; NEJM 2000*

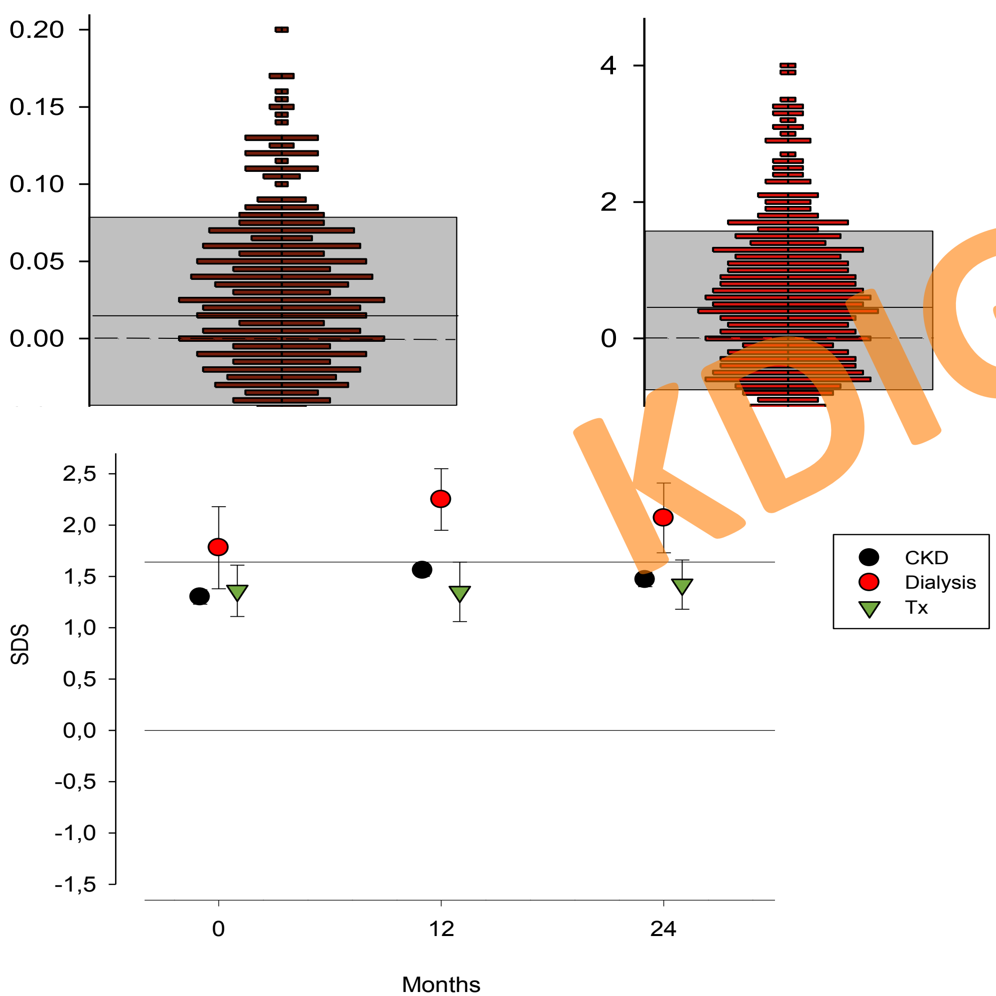


| Dependent variable | Independent variable | β | $R^2$ | P |
|---|---|---|---|---|
| Final CACS | Final Ca×P product | 0.880 | 0.736 | 0.004 |
| CAC progression[a] | Final albumin | −0.811 | 0.601 | 0.009 |

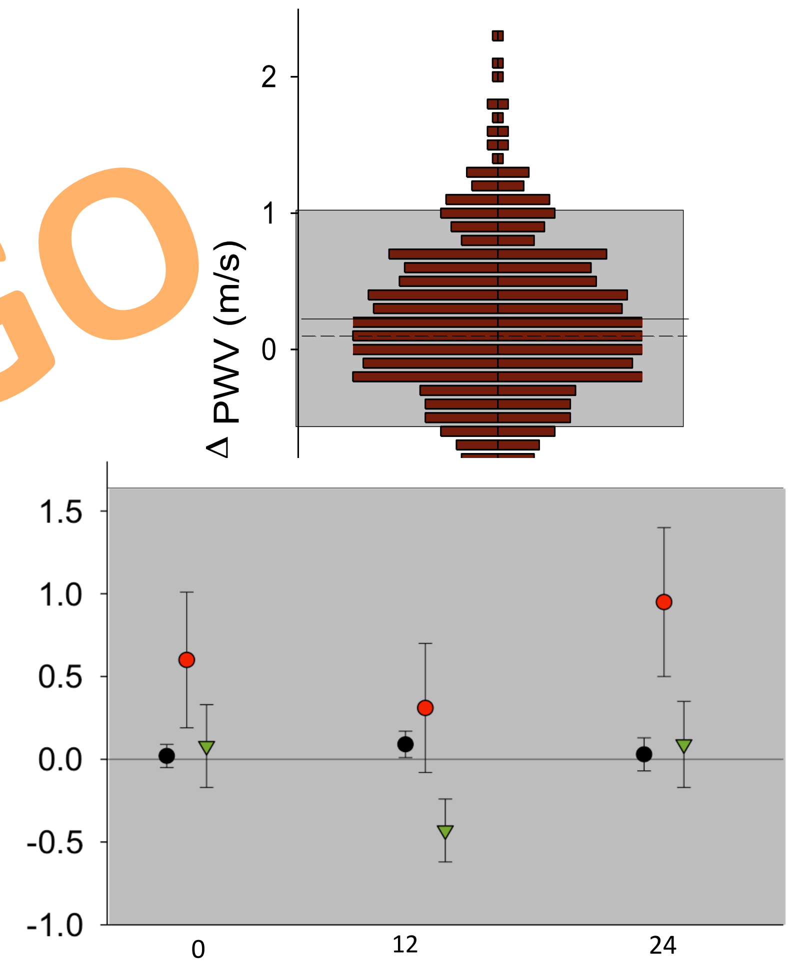
*Civilibal et al; Ped Nephrol 2010*

# Evolution of cIMT and PWV

IMT Progression within 1 Year of Follow-up



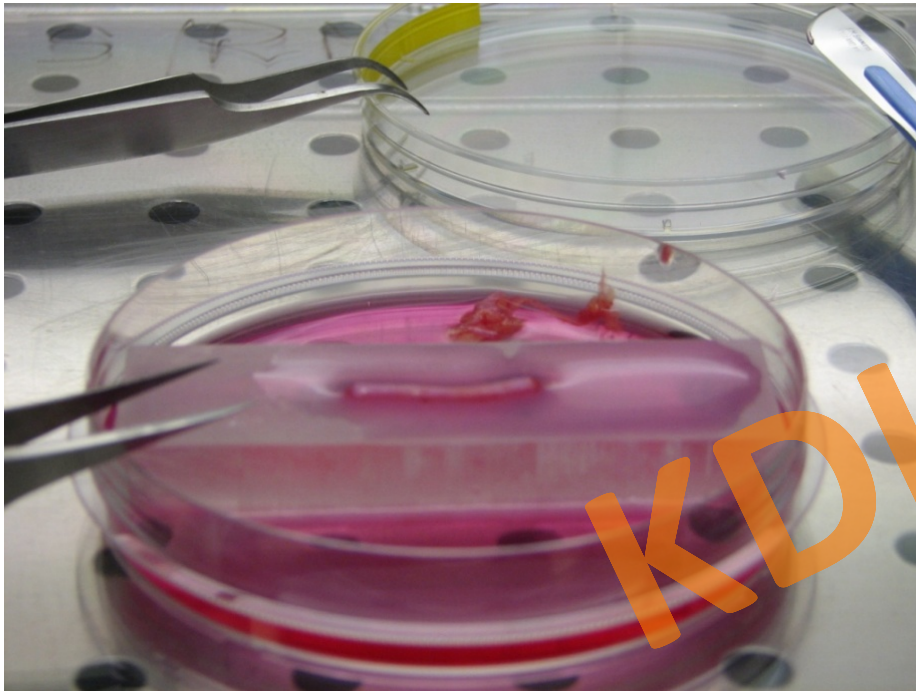

PWV Progression within
1 Year of Follow-up

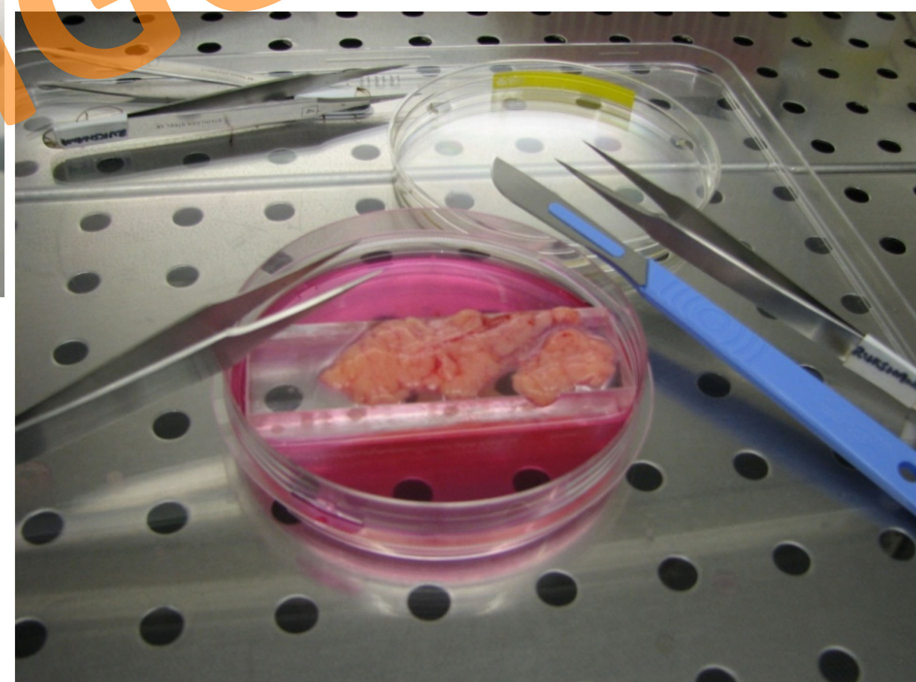





*Slide courtesy of Prof Schaefer*

# An arterial biopsy model

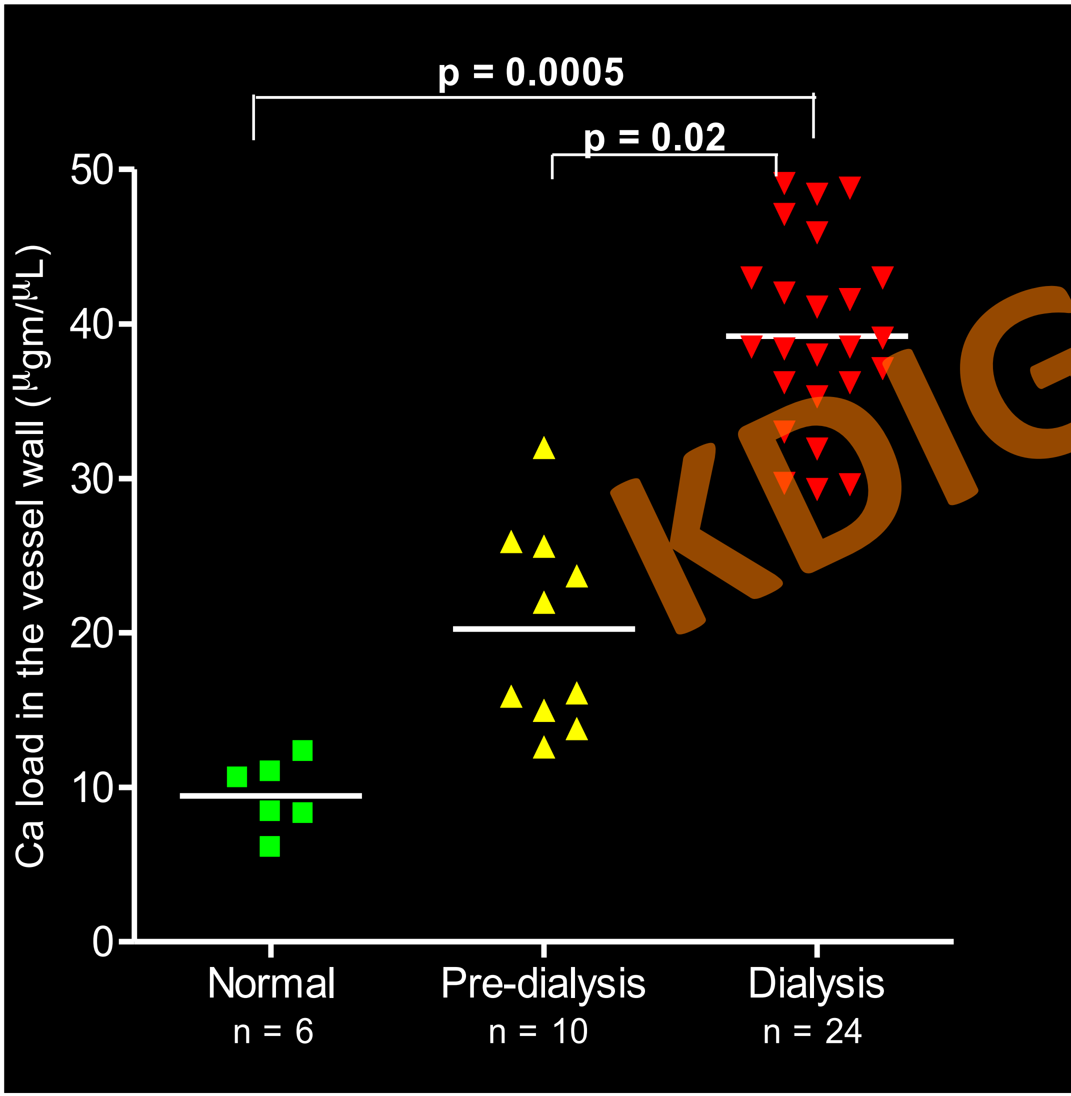




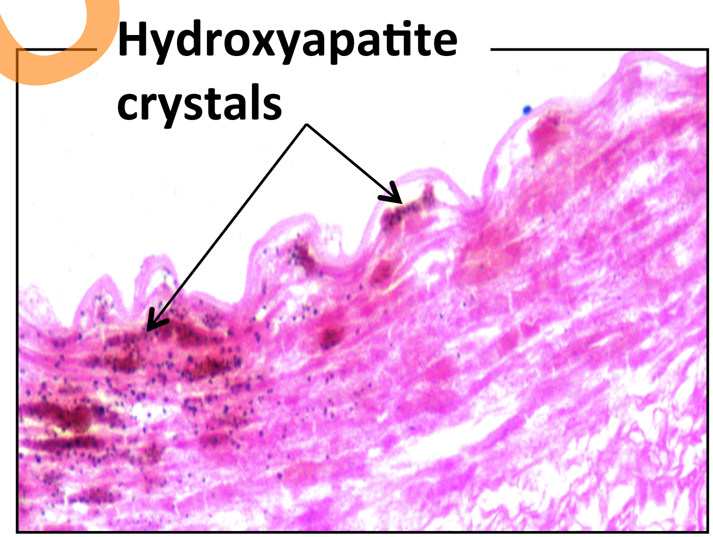


*Shroff et al, Circulation 2008; JASN 2010; JASN 2013*

# Ca accumulation in vessels begins in pre-dialysis CKD



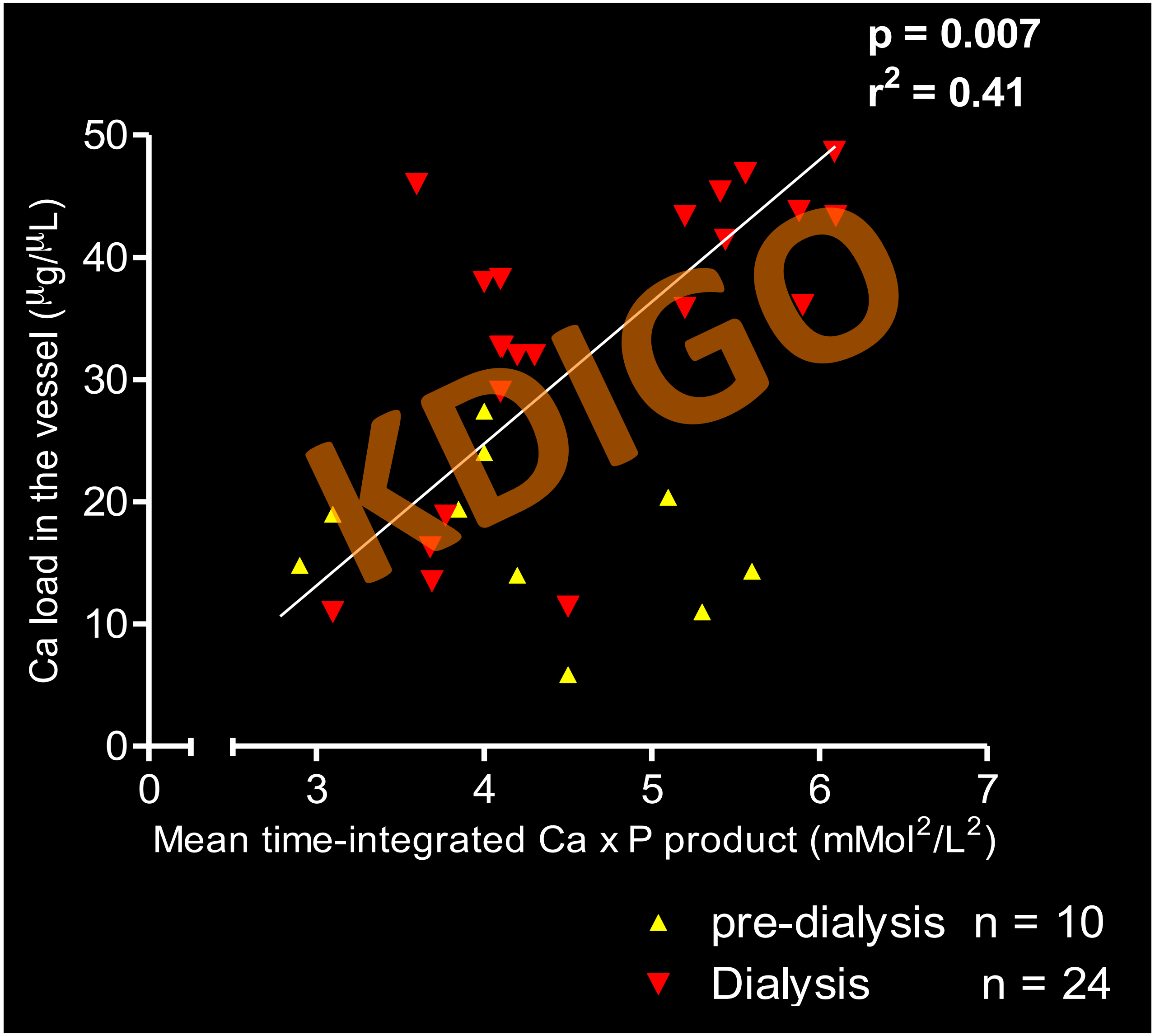

Histological changes in the Vessels were only seen in dialysis patients



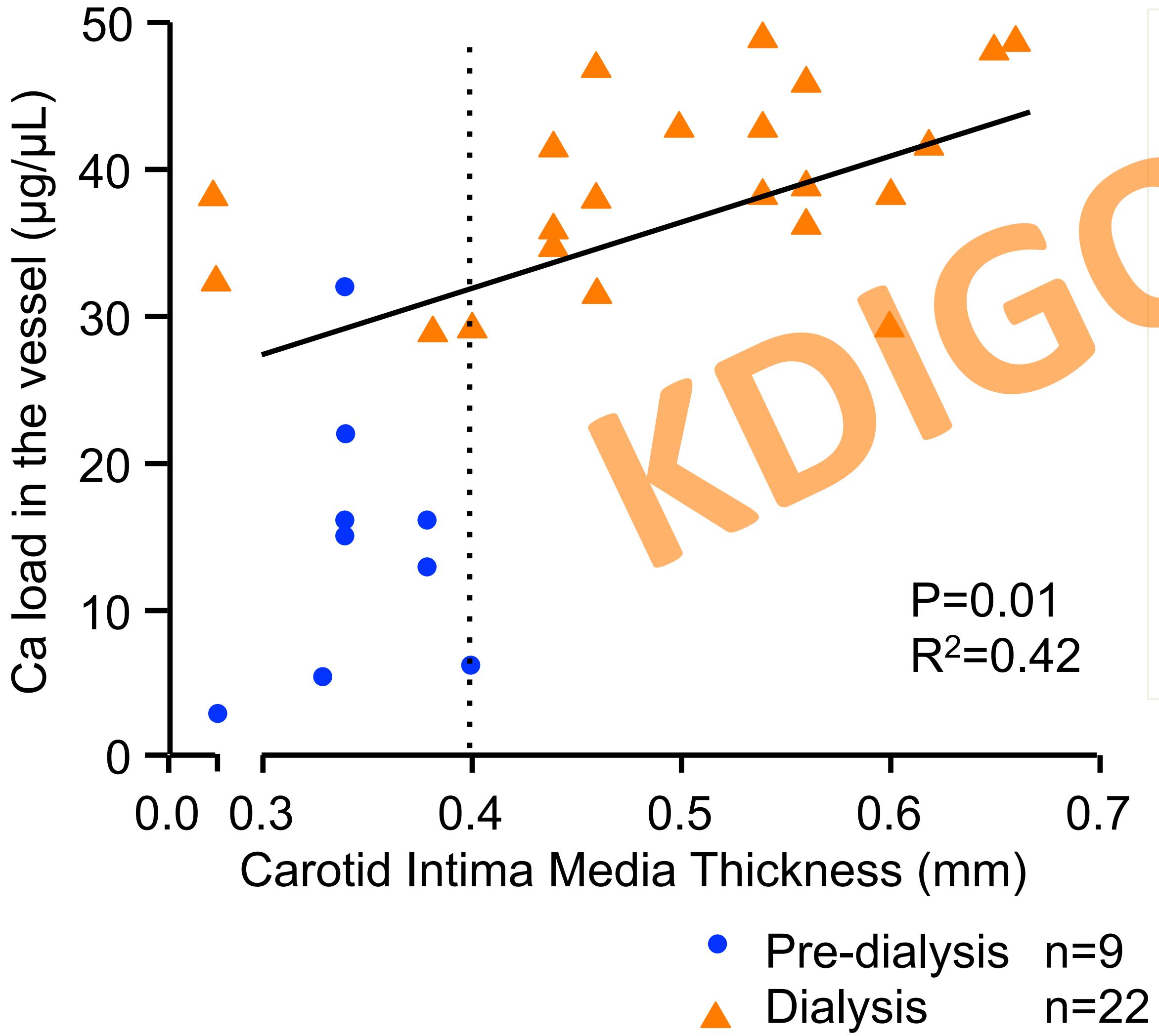

**No inflammation**

*Shroff et al: Circulation 2008*

# Calcification is associated with Ca x P levels



# Ca load correlates with carotid IMT




**Pulse wave velocity**

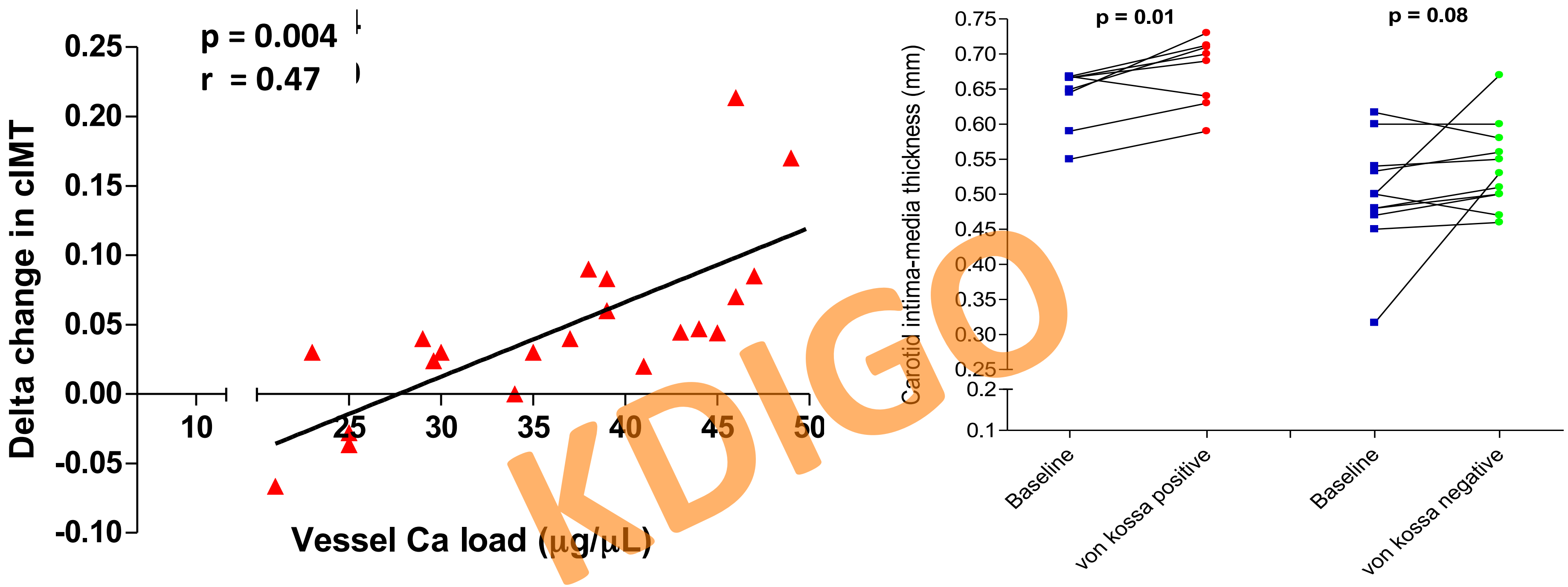
**In 2 /31 patients**

**Coronary calcification on CT scan**

**In 2 /31 patients**

*Shroff et al; Circulation 2008*

# Calcification progression is determined by vessel calcium load





**Associations with cIMT progression**

- Baseline vessel Ca load r = 0.47
- Baseline 25-OH D level r = -0.22
- Mean time-averaged P r = 0.61
- Δ PTH r = 0.17
- Δ Fetuin-A levels r = 0.11

**No associations with**

- Serum calcium
- FGF-23 or s-klotho
- Osteoprotegerin

# Conclusions – vascular studies

- Vascular changes begin in pre-dialysis CKD stage 3b (or earlier) and progress rapidly on dialysis
- Serum phosphate is associated with progression of vascular disease (cIMT and calcification)
- 4C and CKiD studies may soon provide markers of CVD progression

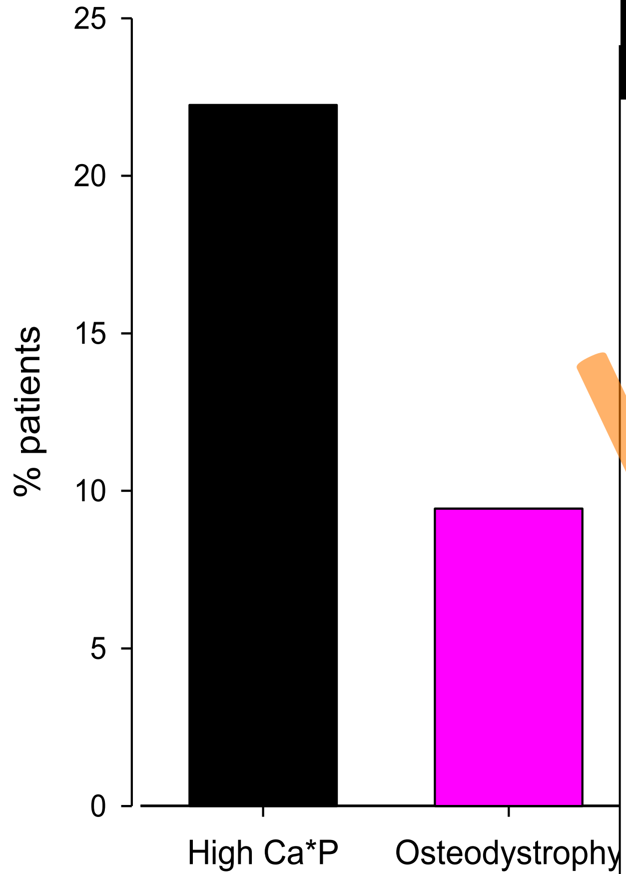
# Bone disease in children with CKD



KDIGO 2009

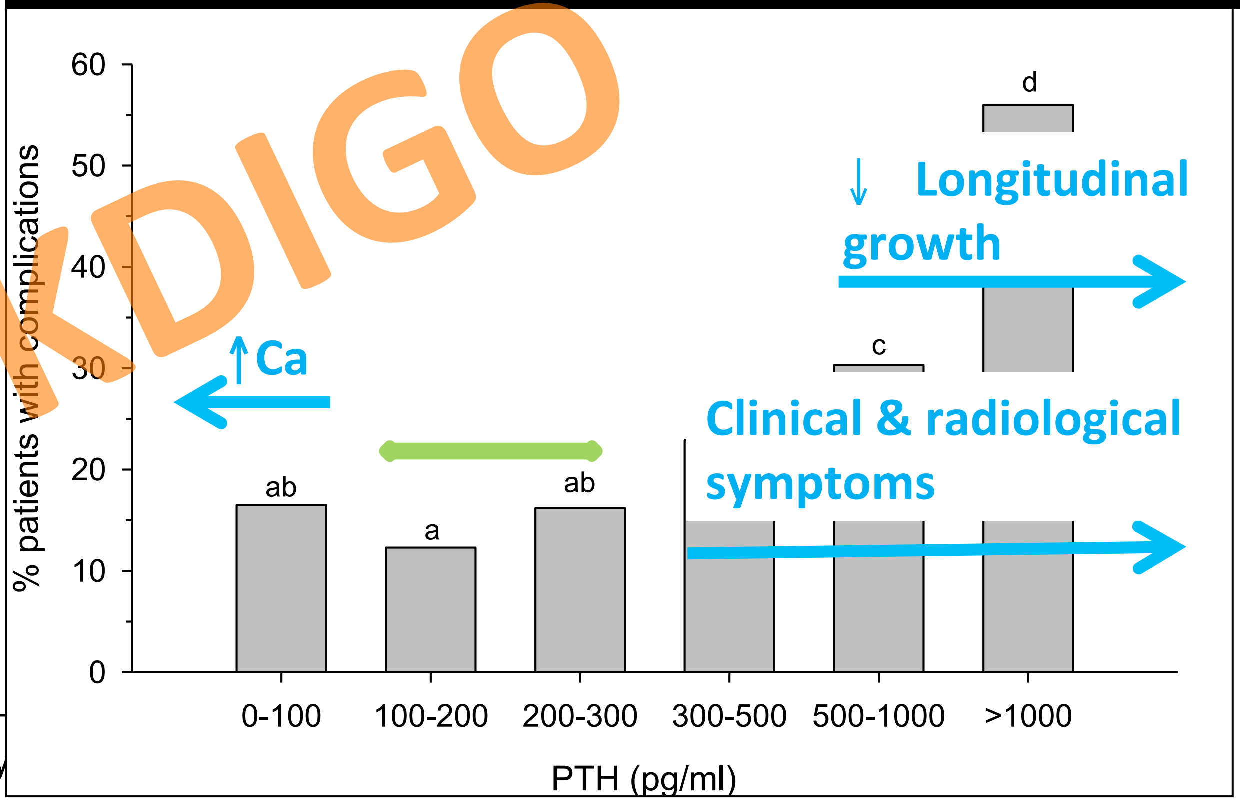
We recommend that infants with CKD 2-5D have their lengths measured at least quarterly, while children with CKD 2-5D should be assessed for linear growth at least annually (1B)

# Bone disease in PD patients




n = 900 children on PD

## PTH levels and MBD




*IPPN Registry data - Borzych et al. Kidney Int 2010*

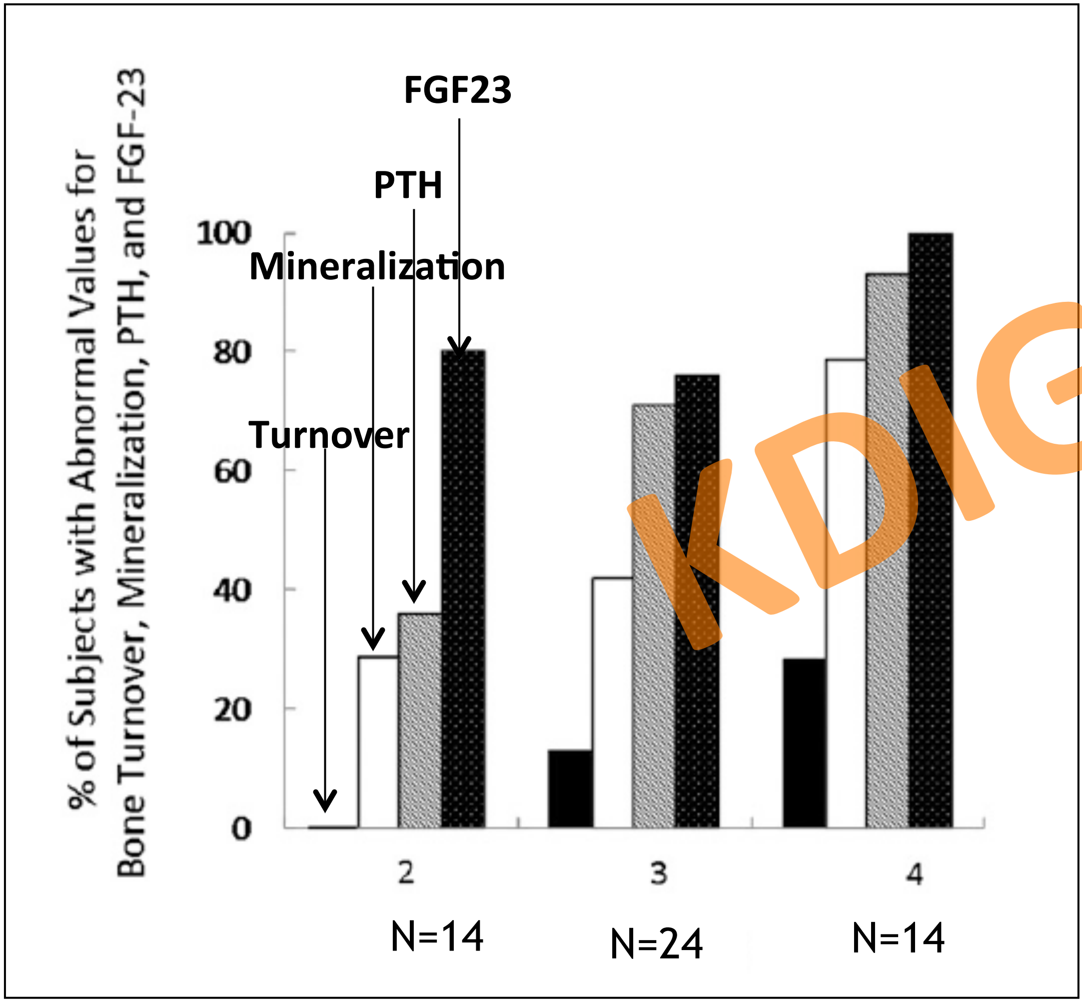
# Associations with abnormal mineralization

| Turnover (BFR/BS) | Mineralization (OV/BV + OMT) | Serum Calcium (mg/dl) | Serum Phosphorus (mg/dl) | Alkaline Phosphatase (IU/L) | PTH (pg/ml) |
|---|---|---|---|---|---|
| Low (*n* = 7) | Normal (*n* = 5) | 9.6 ± 0.4 | 8.2 ± 0.6 | 197 ± 26 | 116 ± 15 |
| | Abnormal (*n* = 2) | 8.1 ± 2.0 | 8.2 ± 2.2 | 250 ± 160 | 282 ± 162 |
| Normal (*n* = 62) | Normal (*n* = 39) | 9.6 ± 0.1 | 6.0 ± 0.2 | 198 ± 16 | 286 ± 38 |
| | Abnormal (*n* = 23) | 8.9 ± 0.2 | 5.9 ± 0.3 | 243 ± 41 | 477 ± 68 |
| High (*n* = 92) | Normal (*n* = 39) | 9.2 ± 0.2 | 6.2 ± 0.2 | 340 ± 31 | 587 ± 58 |
| | Abnormal (*n* = 53) | 8.8 ± 0.1 | 6.5 ± 0.2 | 506 ± 39 | 924 ± 67 |



**↓ serum calcium and ↑ PTH in patients with defective mineralization, irrespective of bone turnover**

# Bone biopsies - ↓ Ca and ↑ PTH are associated with defective mineralization




**Abnormal mineralization**

- ↓ serum calcium
- ↑ PTH
- FGF-23: NS
- Acidosis: NS



Bone biopsies in 52 children with CKD 2-4
Age - 2 to 21 years

*Wesseling-Perry et al; cJASN 2012*

# Tibia QCT - ↓ Ca and ↑ PTH are associated with decline in cortical BMD

### Cross-sectional

- 171 patients, age 5-21 yrs
- CKD 2-5D

| | β (95% CI) | p-value |
|---|---|---|
| Calcium (per 1 mg/dl) | 0.31 (0.08, 0.54) | 0.01 |
| 25(OH)D (per 10 ng/ml) | 0.18 (0.01, 0.34) | 0.04 |
| $1,25(OH)_2D$ (per 10%) | -0.07 (-0.10, -0.04) | < 0.001 |
| PTH (per 10%) | -0.02 (-0.04, -0.01) | 0.002 |
| FGF23, underlying renal disease and acidosis were not significant. | | |

### Longitudinal

- After 12 months
- 89 patients

**Decline in cortical BMD Z-scores:**

- Higher baseline $1,25(OH)_2D$
- ↑ΔPTH

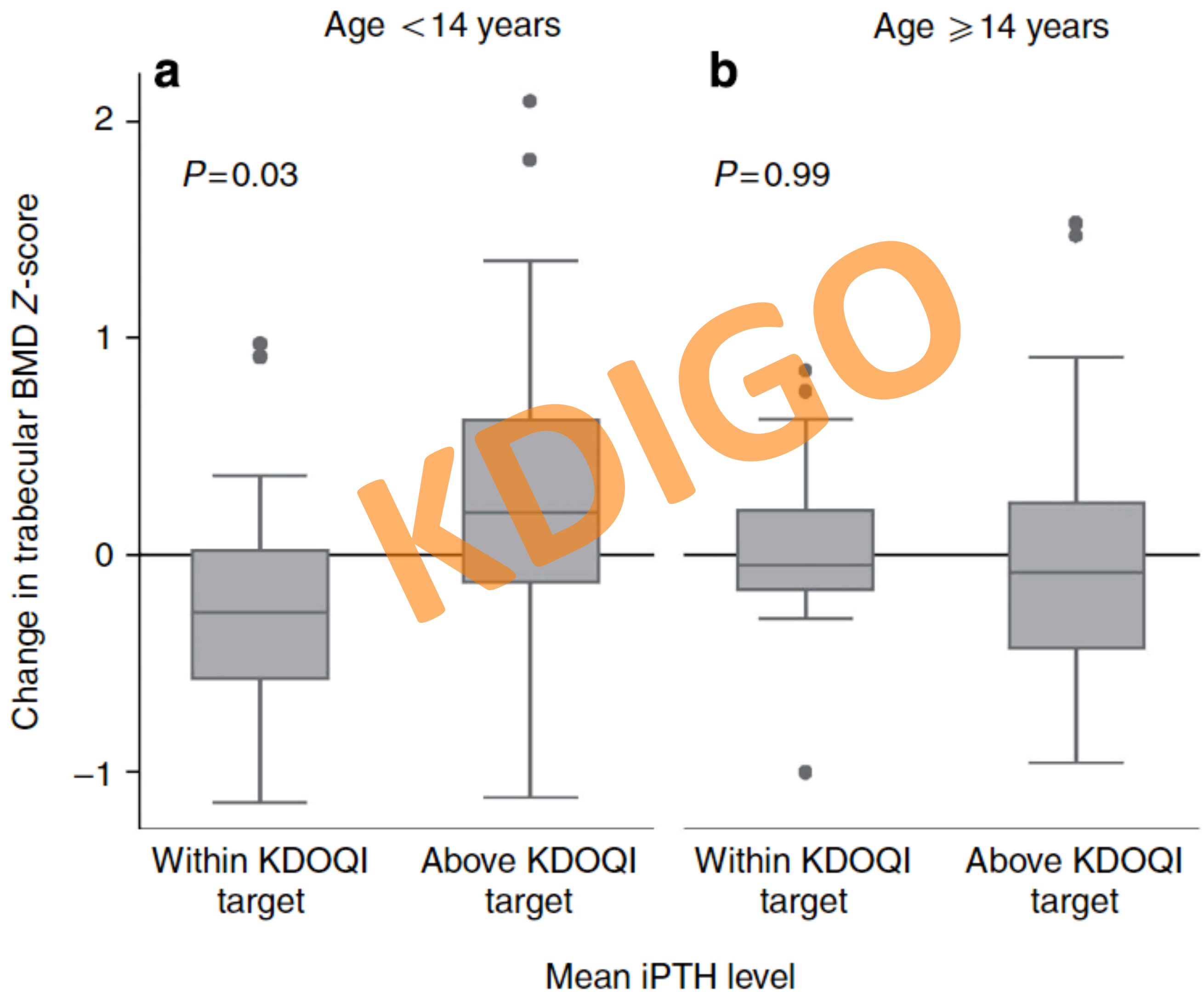
↑Δ Calcium - ↑ cortical BMD

(especially in growing children)

Lower cortical BMD – increased fracture risk (HR 1.75)

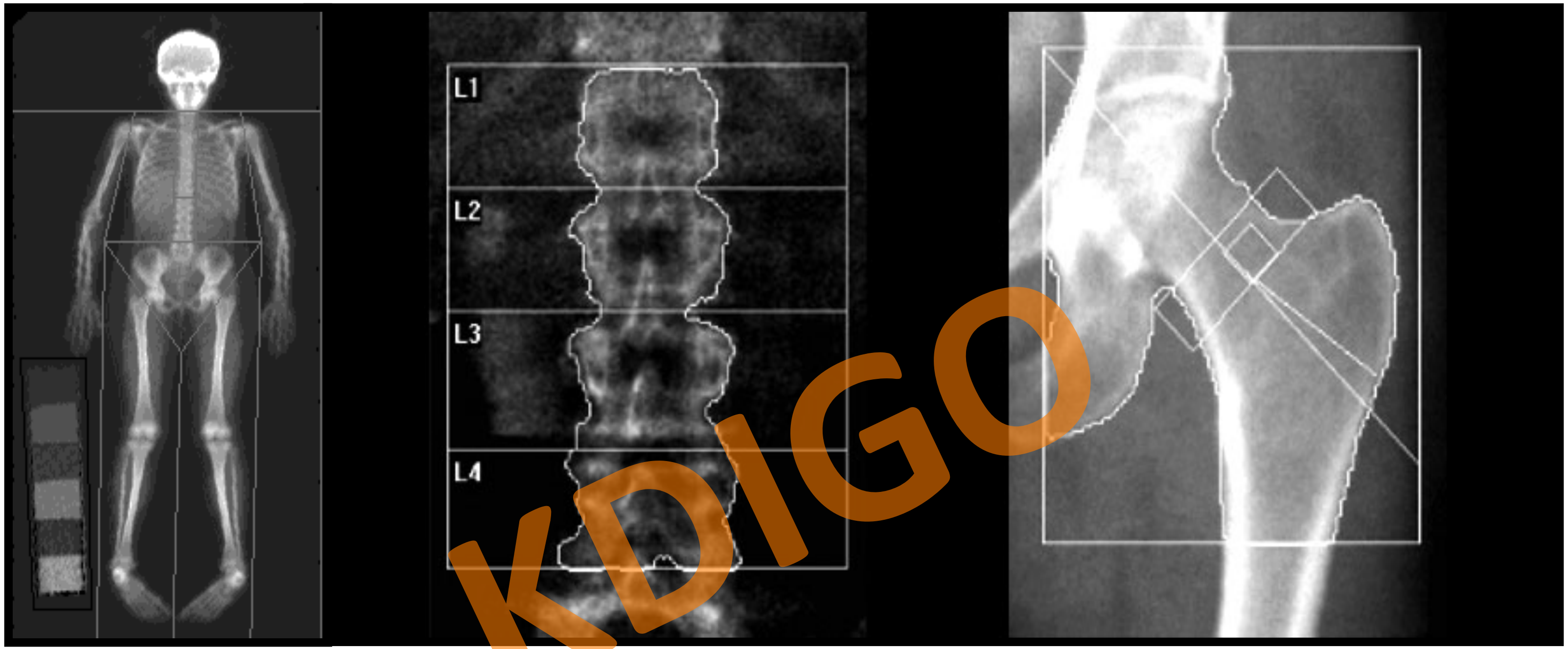
*Denburg, et al. JCEM 2013*

# Tibia QCT - Trabecular BMD




*Tsampalieros, et al. Kidney Int 2012*

# Limitations of DXA in CKD

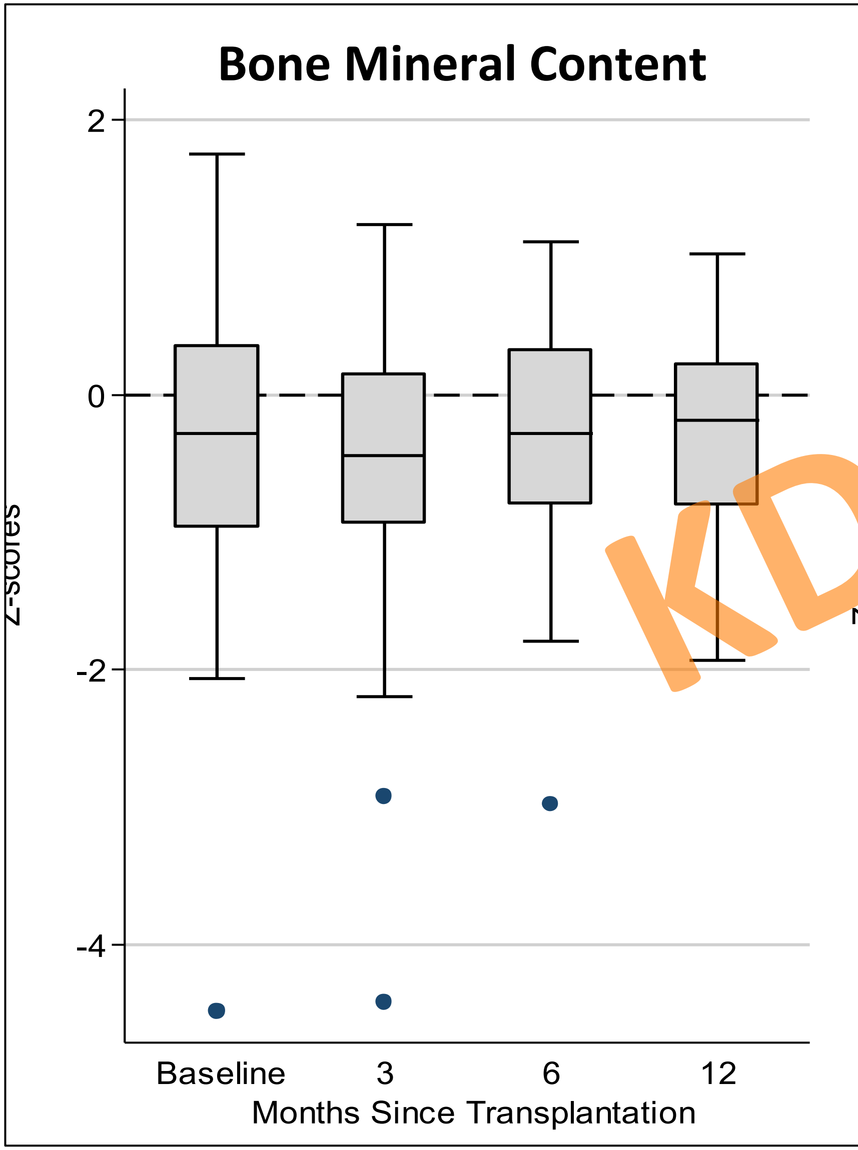



**KDIGO 2009 and ISCD 2007**

**– recommends <u>against</u> routine DXA BMD testing in CKD3-5**

**BMD does not differentiate the type of renal osteodystrophy**

# Whole Body DXA in transplant recipients

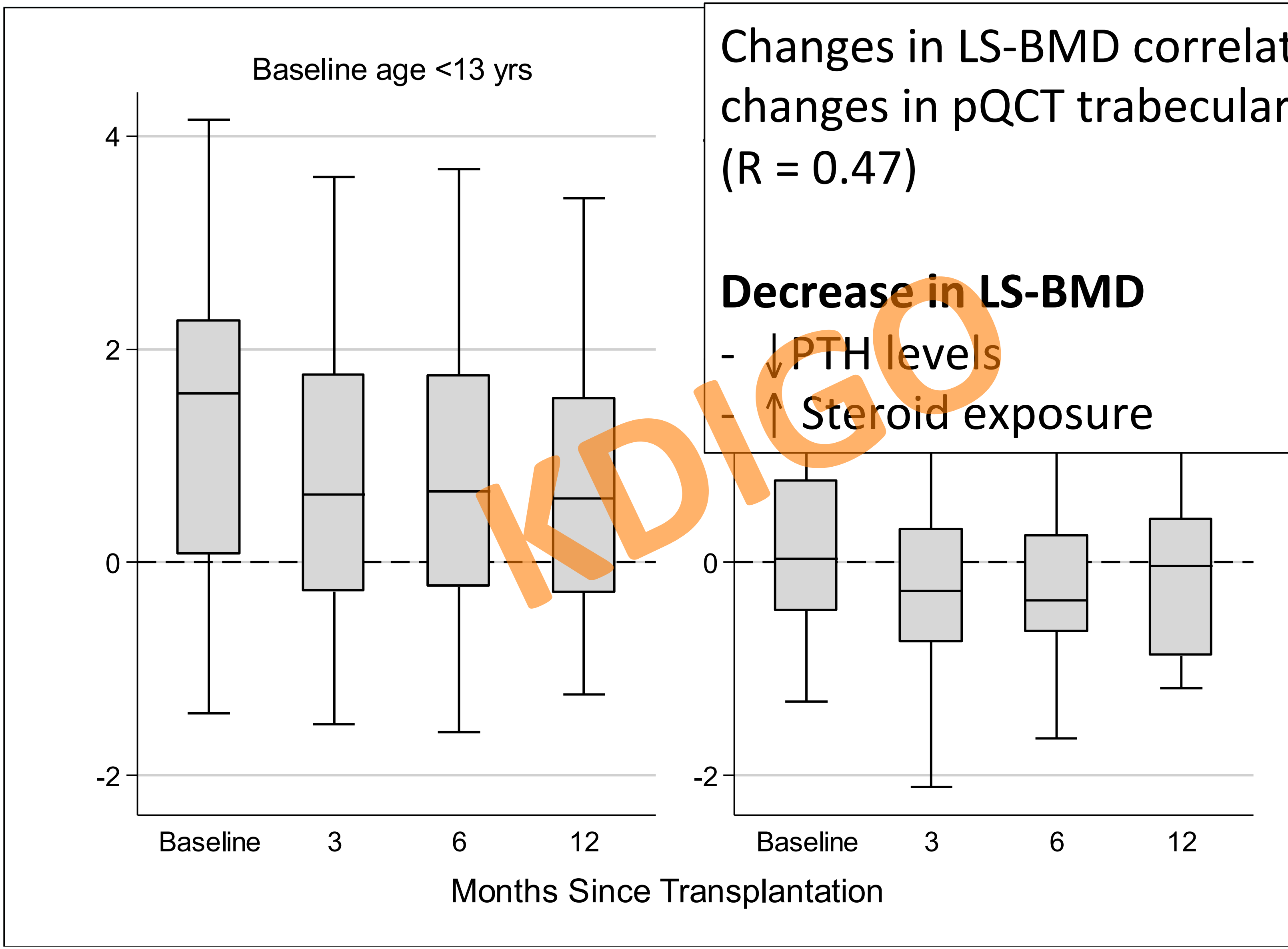



- Whole body BMC Z-scores were correlated with pQCT cortical area Z-scores ($R = 0.77$, $p < 0.0001$) rather than cortical BMD.
- Greater linear growth was associated with greater increases in WB-BMC Z-scores ($p = 0.01$).
- Greater glucocorticoid exposure was associated with greater declines in WB-BMC Z-scores ($p < 0.001$).



*Tsampalieros, et al; Am J Transplant 2013*

# Renal Transplant: Lumbar Spine DXA




Changes in LS-BMD correlated with changes in pQCT trabecular BMD (R = 0.47)

**Decrease in LS-BMD**

- ↓PTH levels
- ↑ Steroid exposure



*Tsampalieros, et al; Am J Transplant 2013*

# Conclusions – bone studies

- Abnormal bone mineralisation occurs early (CKD2) and is associated with low serum calcium and high PTH
- Non-invasive assessment by qCT and DXA may be useful tools in evaluating children with CKD

# In the context of paediatric CKD-MBD

Do we need new guidelines? ✓

Do we need to change existing recommendations / grading of existing recommendations? ✓



Separate paediatric guidelines
or
More precisely address paediatric management within any new guidelines ?