Vitamin D and renal failure facts and fancies

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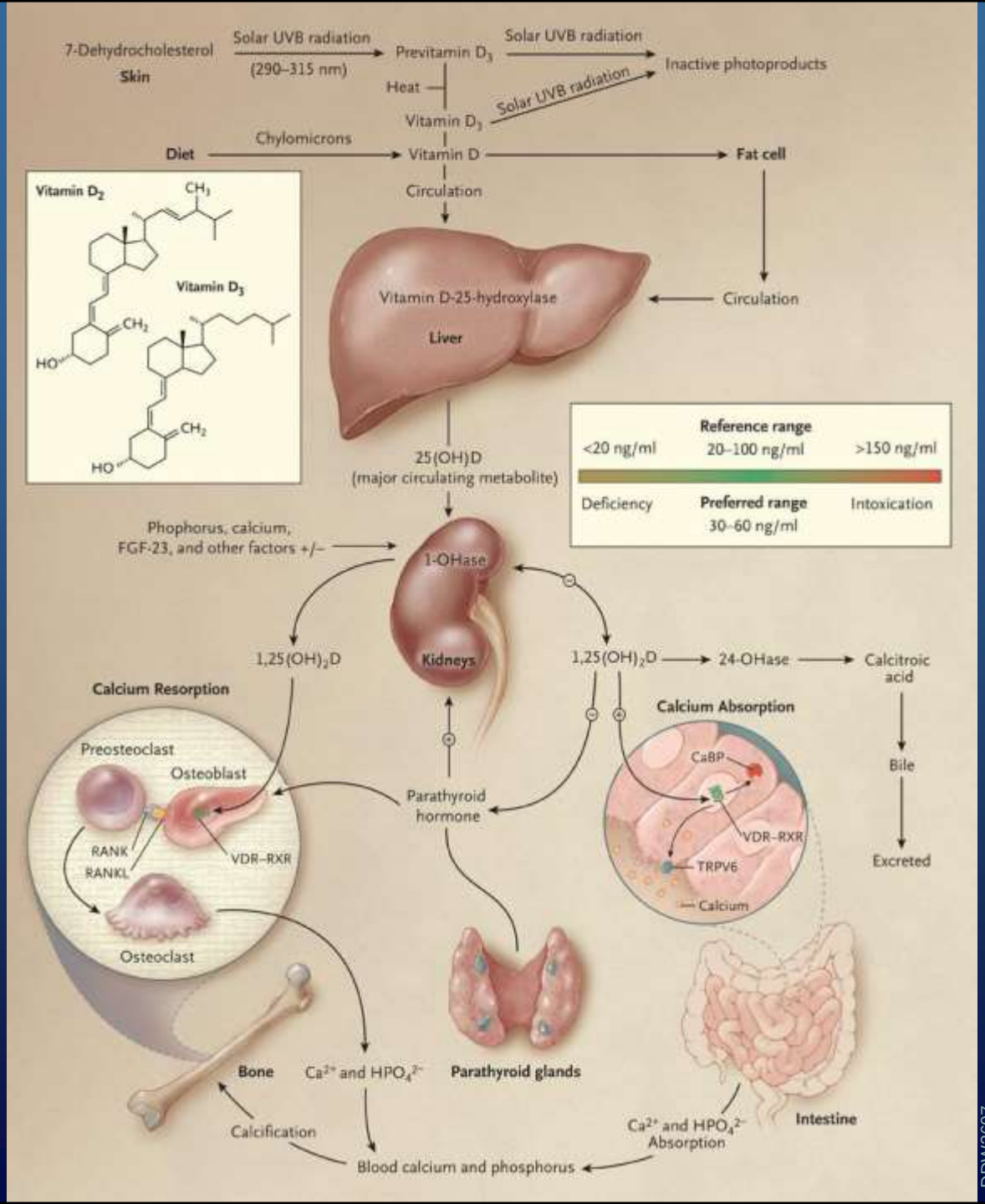
Budapest 2915

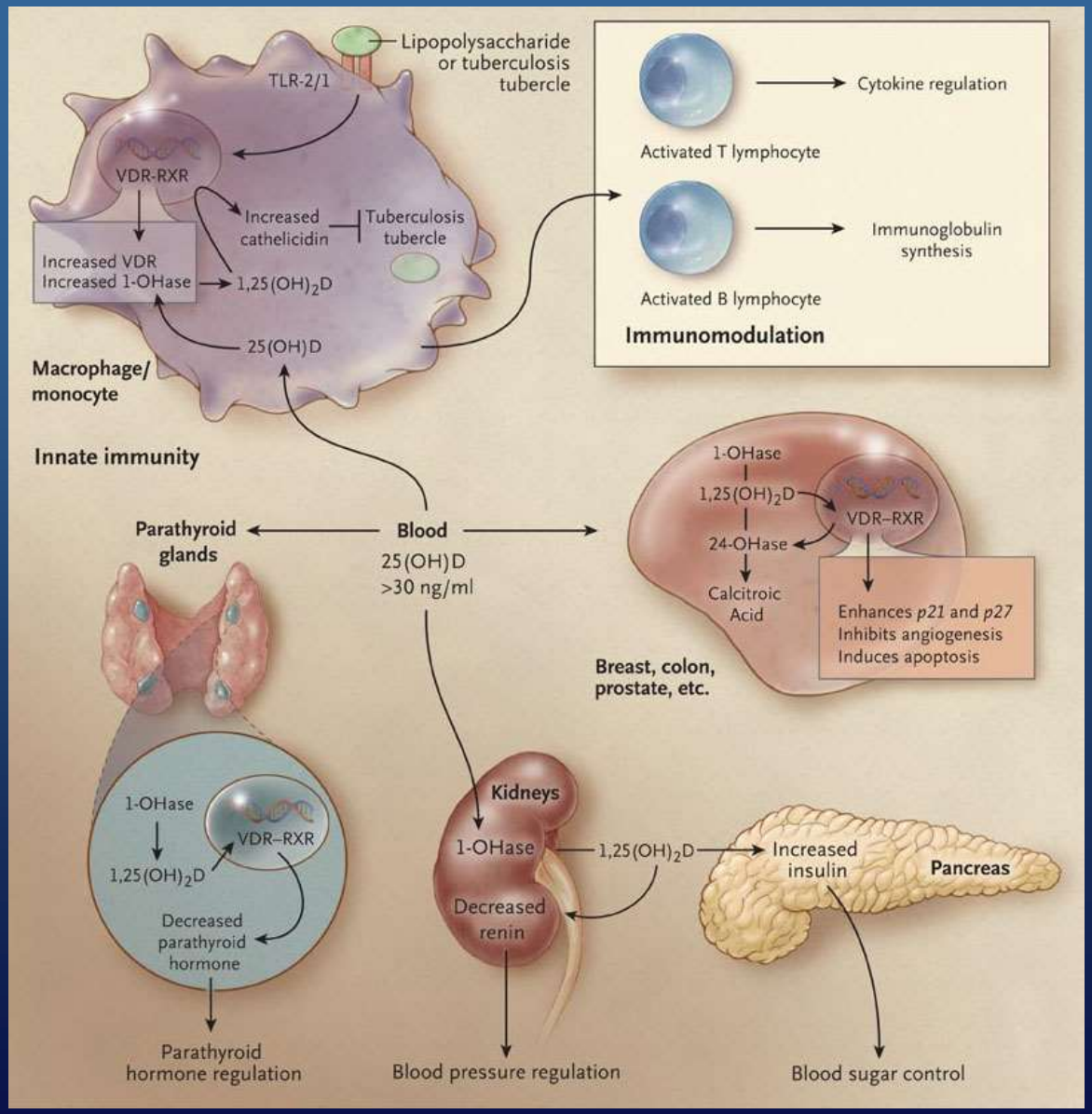
Vitamin D deficiency



Synthesis and metabolism of vitamin D in the regulation of calcium, phosphorus, and bone metabolism

Holick MF: NEJM 357: 266-281, 2007

Vitamin D deficiency

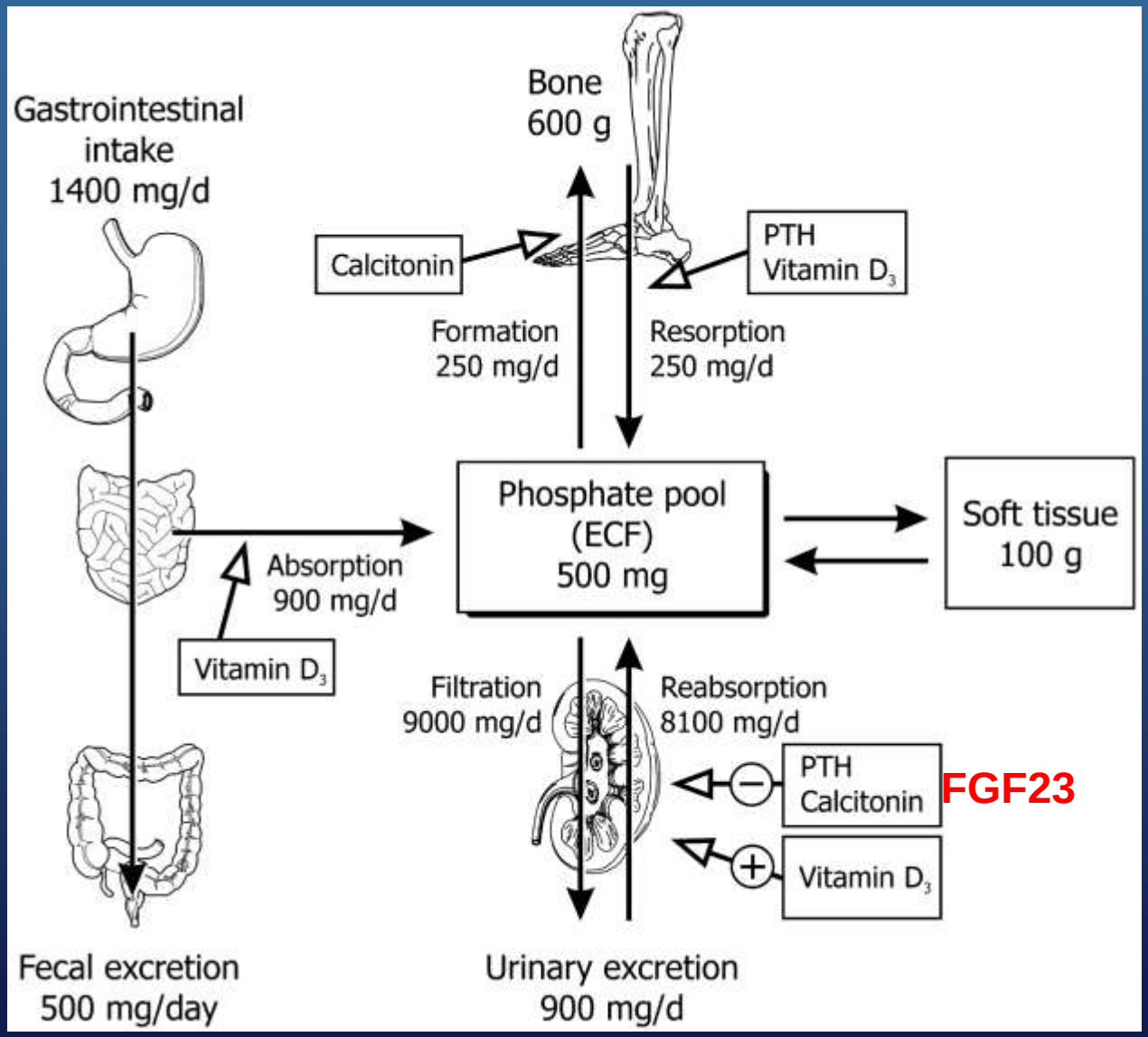


Metabolism of 25-Hydroxy-vitamin D to 1,25-Dihydroxy-vitamin D for Nonskeletal Functions

Holick MF: NEJM 357: 266-281, 2007

DDW3607

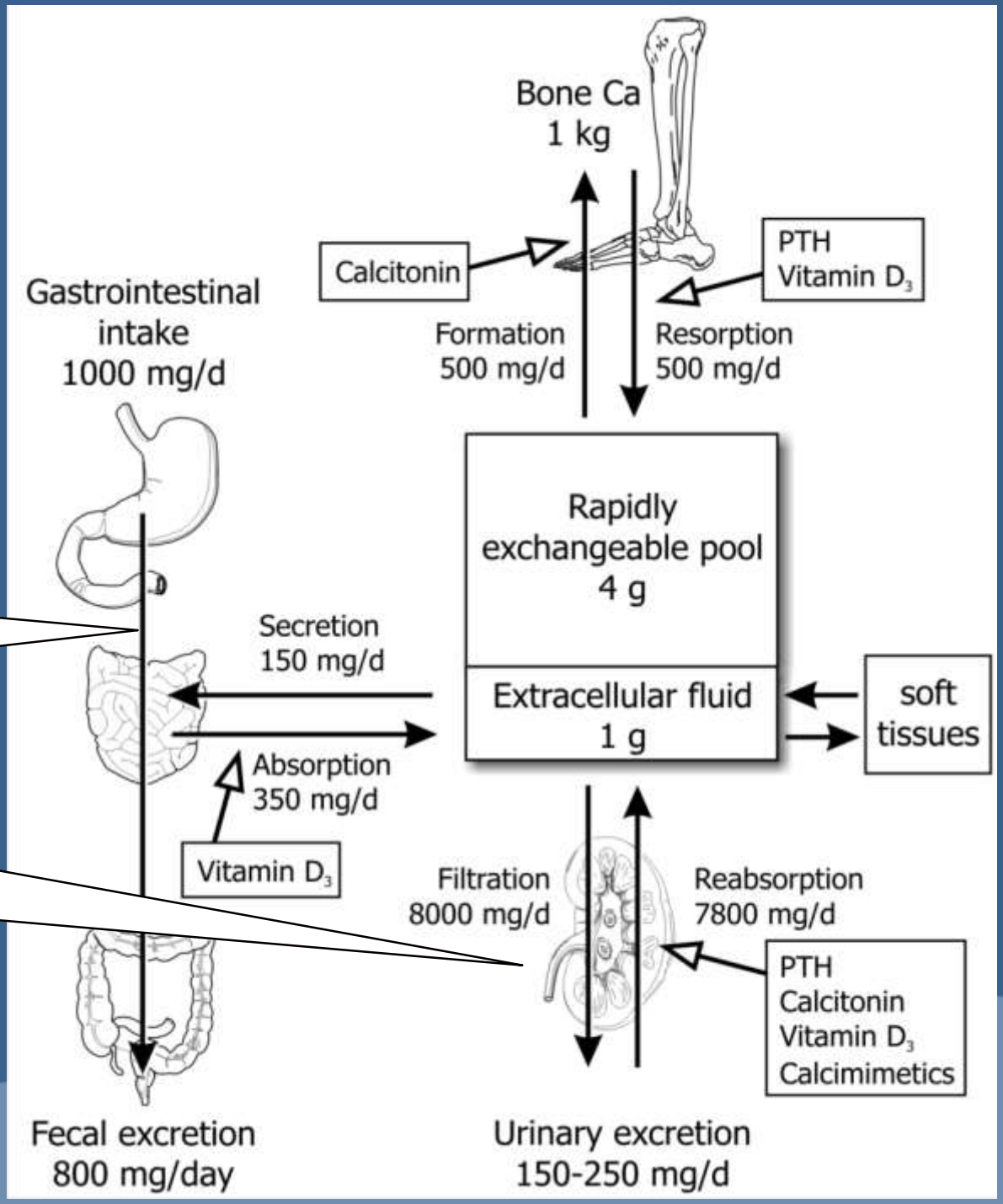
Normal phosphate homeostasis



Behets G, PhD thesis, 2005

DDW3398

Average daily calcium turnover in human

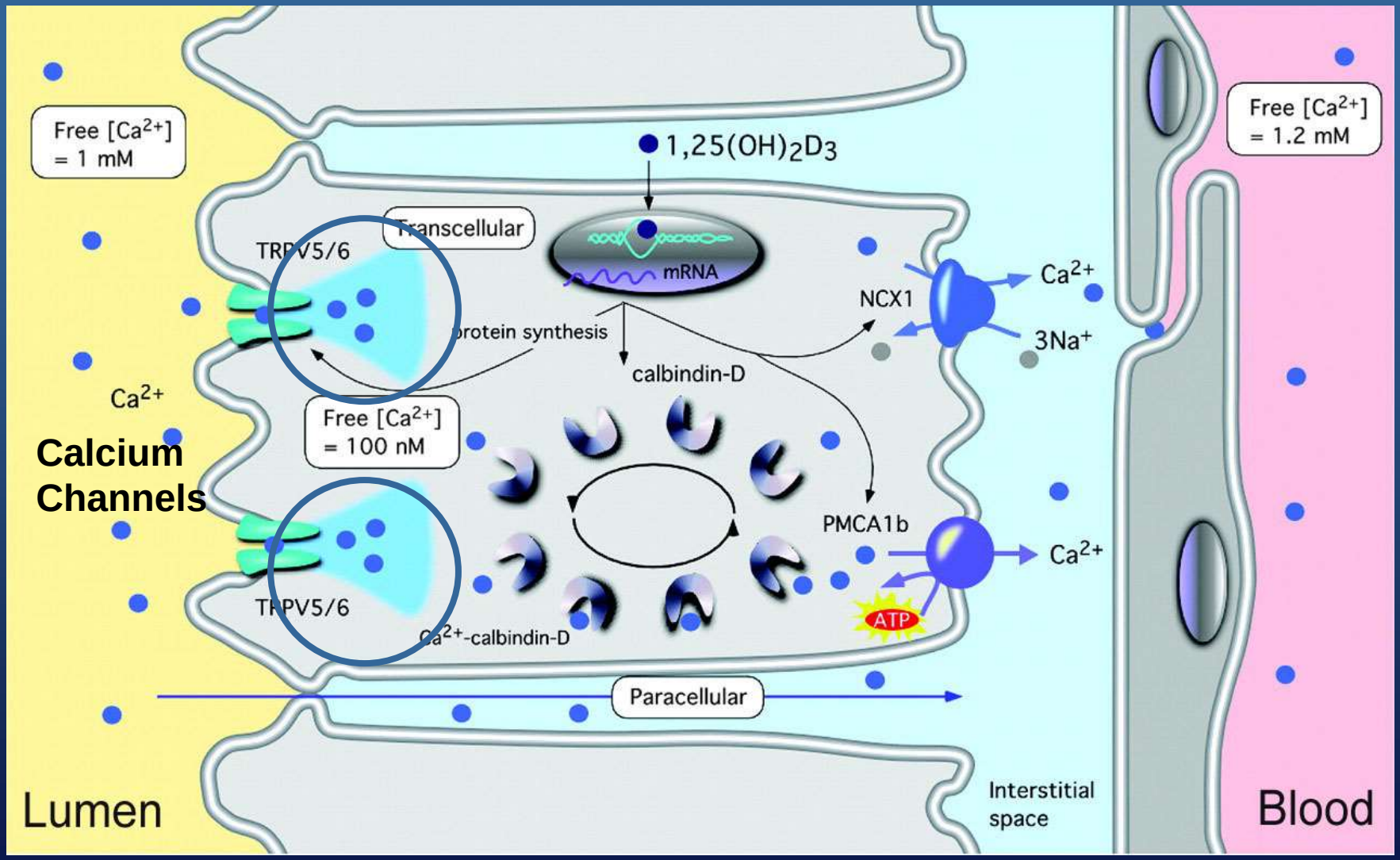


Calcium load in dialysis:
10-15 meq/d (400-600 mg/d)
when using Ca containing P binders

The rate of active Ca^{2+} reabsorption is controlled by the calciotropic hormones, i.e. parathyroid hormone, calcitonin and 1,25-dihydroxyvitamin D3.

Calcium absorption across epithelia

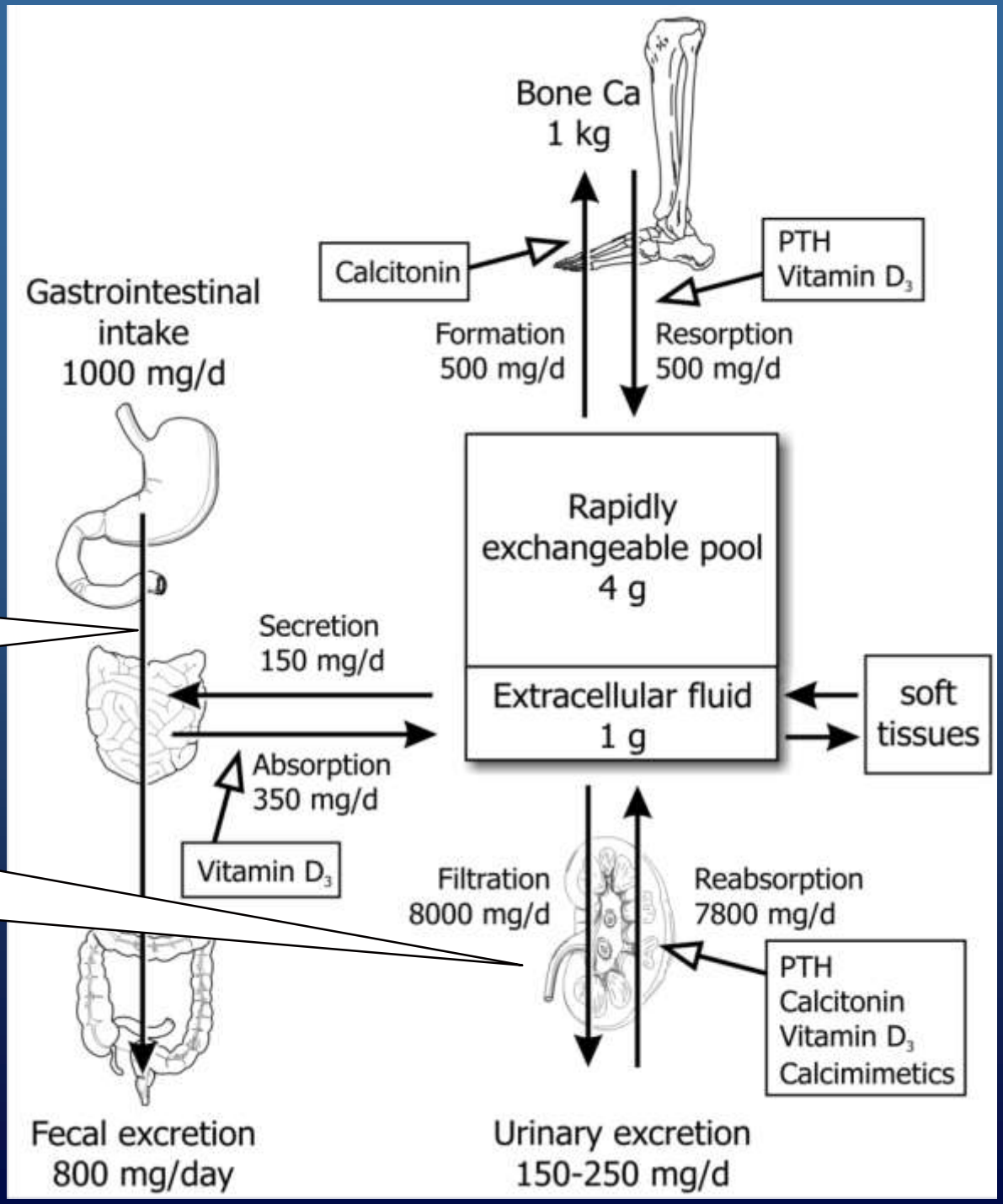
Mechanism of epithelial Ca^{2+} transport



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

Calcium sensing receptor

Average daily calcium turnover in human



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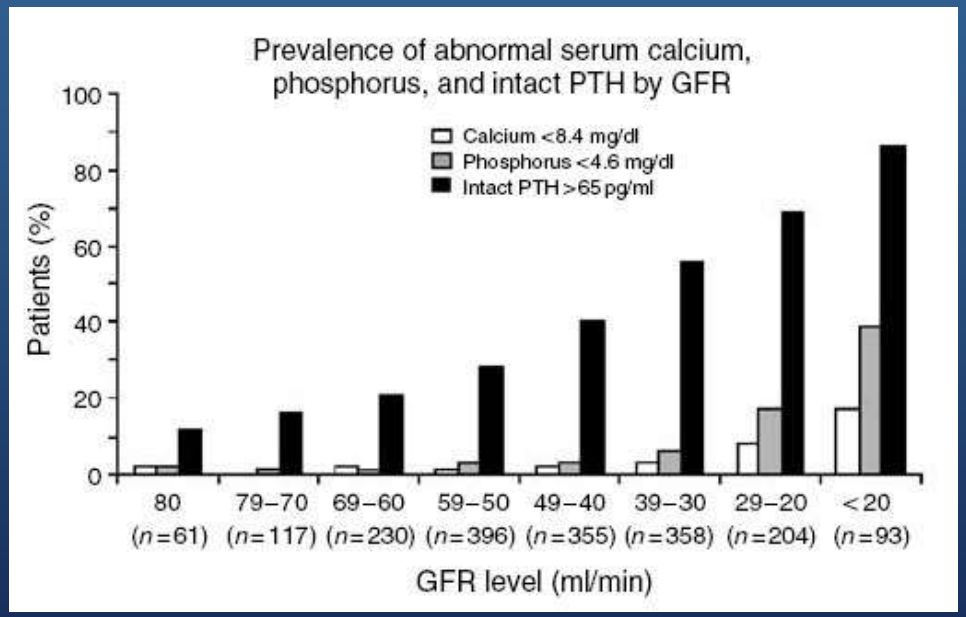
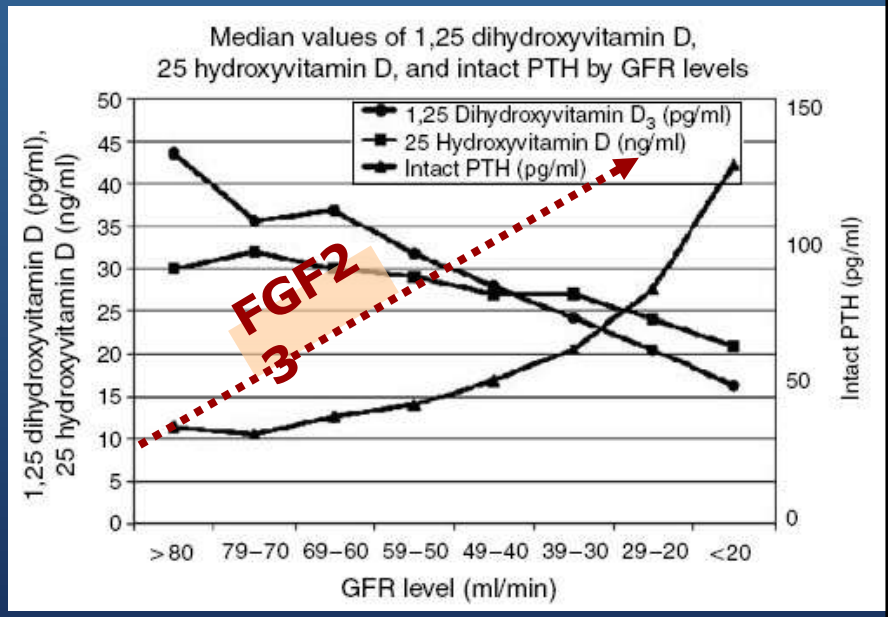
Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: *Results of the study to evaluate early kidney disease*

In dialysis :adynamic bone disease highly prevalent





Decrease in Vit D receptors

Decrease in Ca sensing receptors on PTH gland

Early increase of FGF23

No relation to the renal mass

Hypocalciuria (<100mg/24hrs)

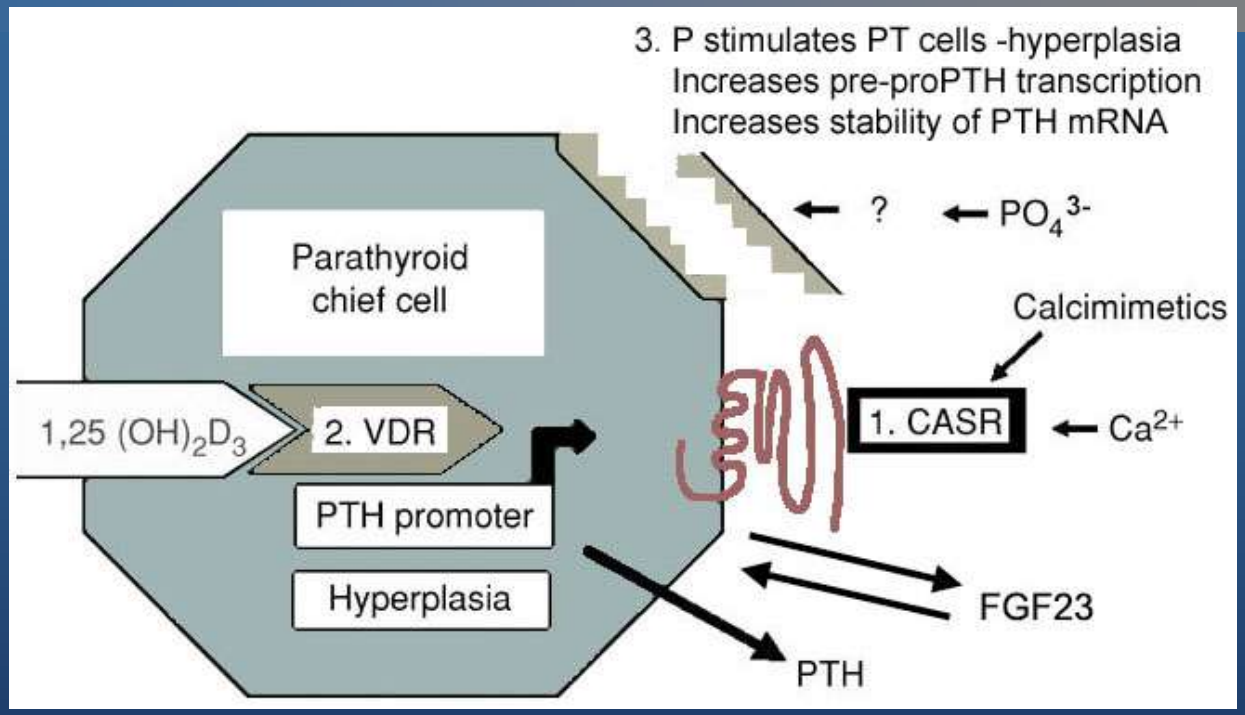
Tendency to hypocalcemia

2

SECUNDARY HYPERPARATHYROIDISM, NEGATIVE CALCIUM BALANCE

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

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 (inhibits PTH synt)
3. Uncharacterized phosphate sensor , stimulates PTH synthesis
4. FGF23 is a negative regulator of parathyroid function

Universiteit Antwerpen

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

Importance of calcium dependent signaling

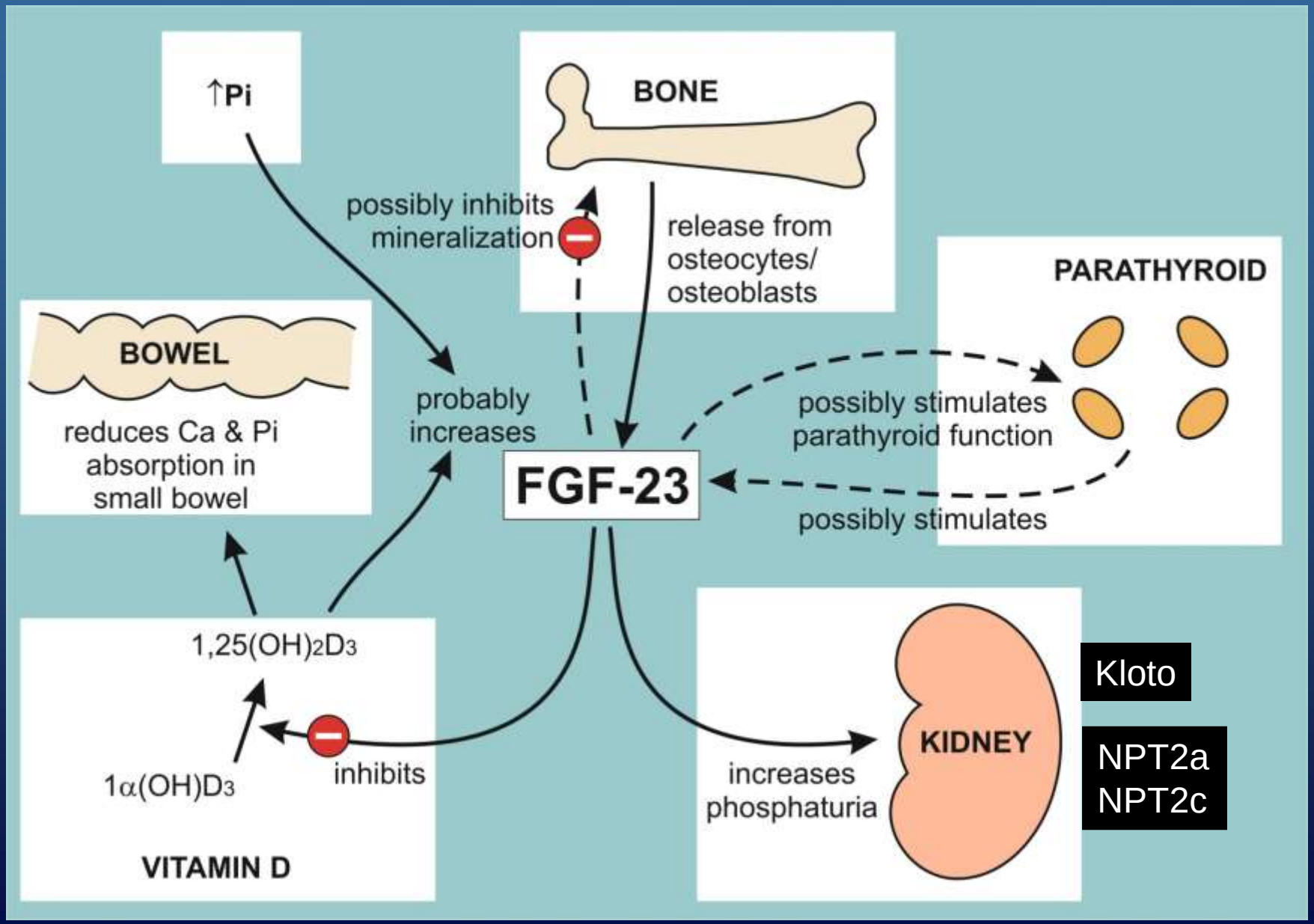
Vitamin D dependent pathways play a 2ary role

	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, but Ca administration almost everything

Fibroblast growth factor 23

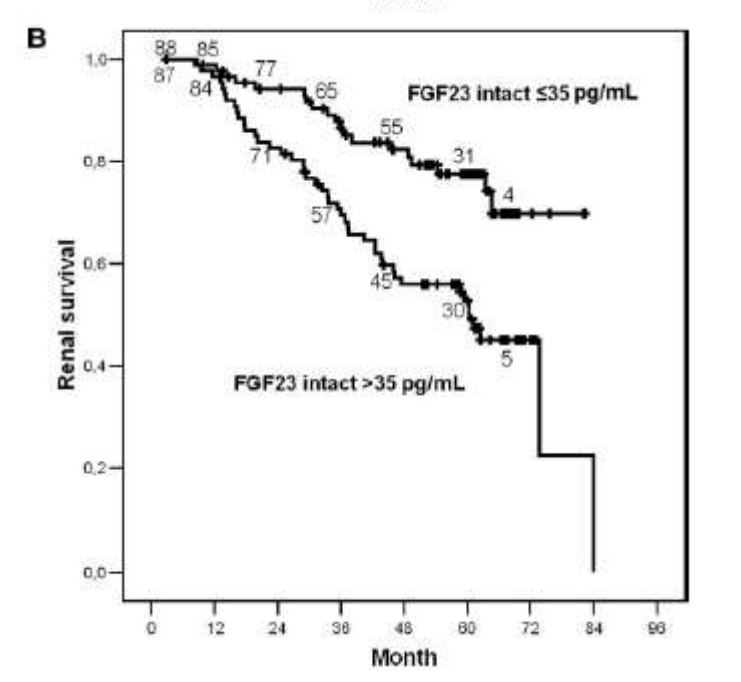


Régulation de la Phosphatémie par l'action Concertée de FGF23/FGFR/Klotho

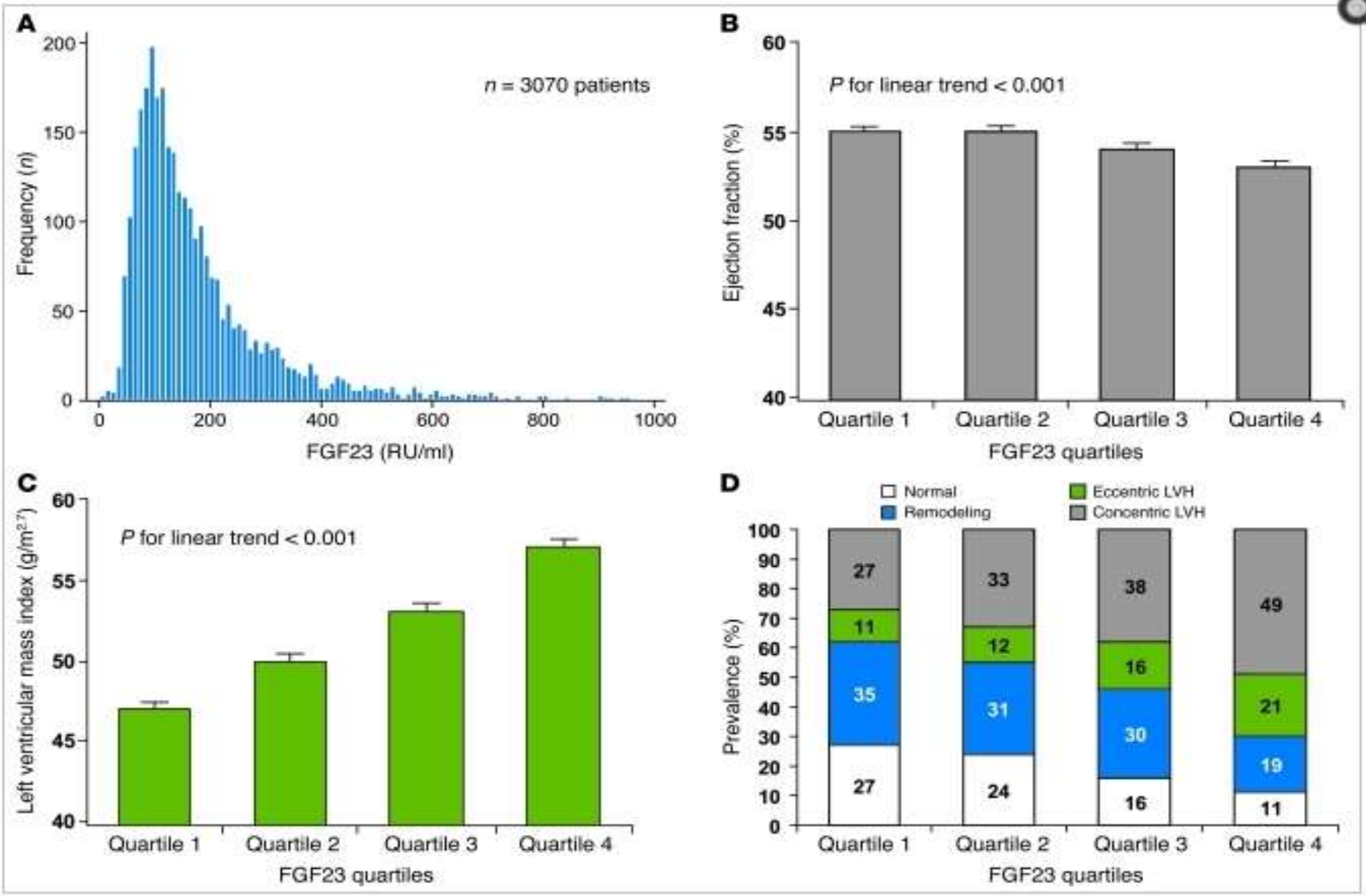
Fibroblast Growth Factor 23 (FGF23) Predicts Progression of Chronic Kidney Disease: The Mild to Moderate Kidney Disease (MMKD) Study

Danilo Fliser,* Barbara Kollerits,† Ulrich Neyer,‡ Donna P. Ankerst,†§ Karl Lhotta,‖ Arno Lingenhel,† Eberhard Ritz,¶ and Florian Kronenberg;† for the MMKD Study Group

	Progresseurs	Non Progresseurs
FGF23 (pg/ml)	35± 58	69± 70
Phosphate (mmol/ml)	1.04 ± 0.38	1.25 ± 0.27
PTH (pg/ml)	6± 5	22 ± 20

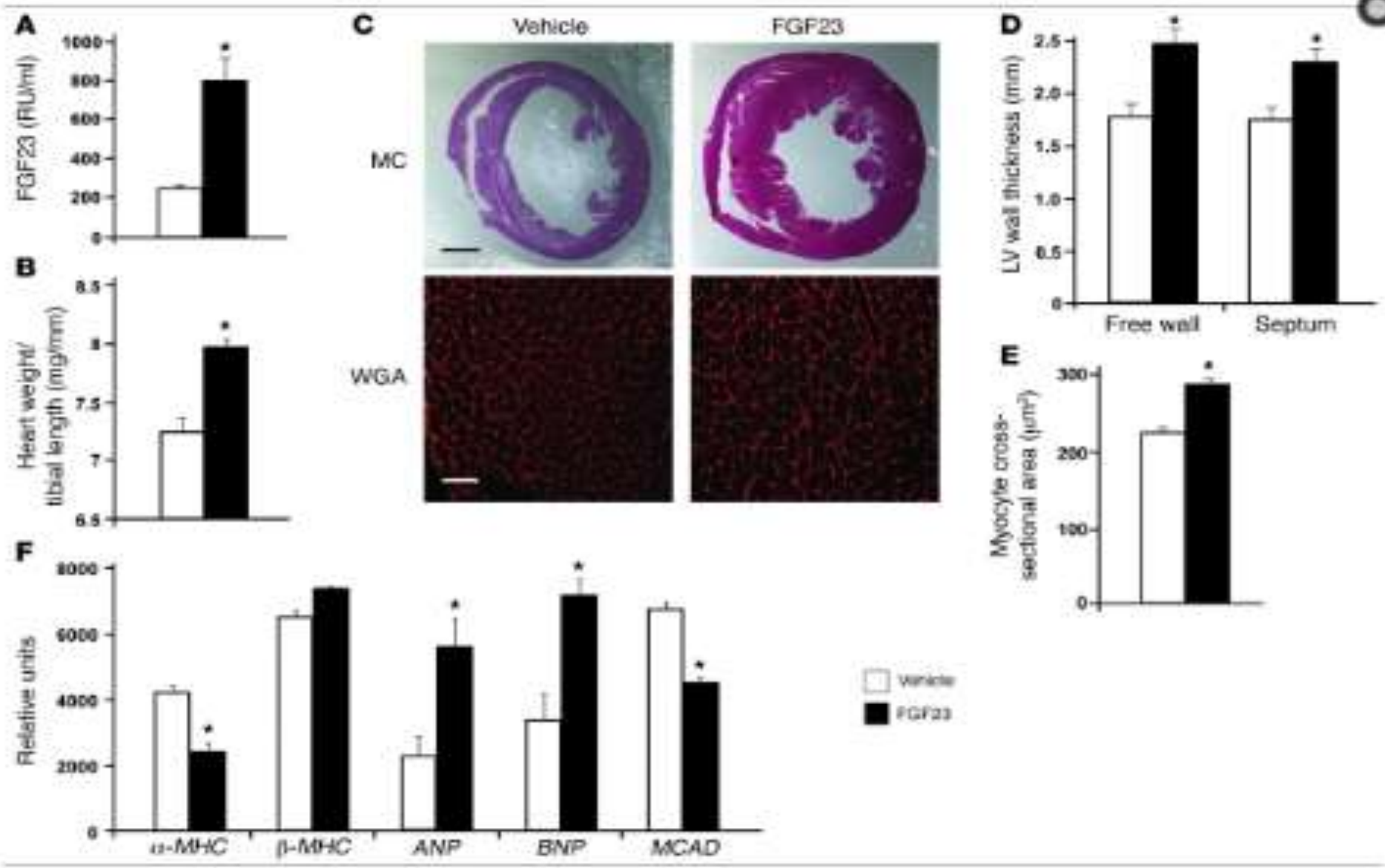


Fliser D et al. JASN, Early online edition, 2007



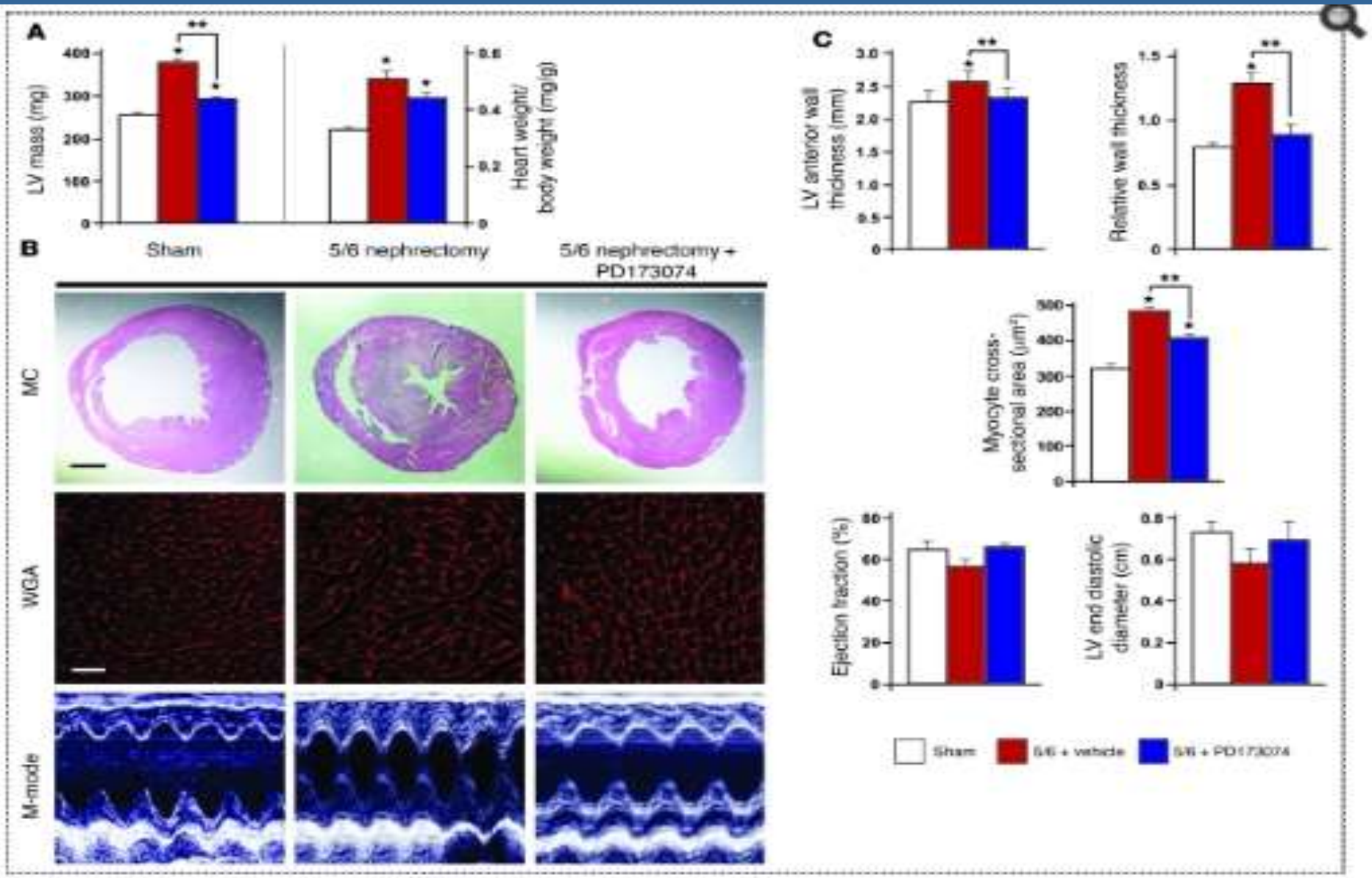
Elevated circulating FGF23 levels are associated with LVH in patients with CKD.

JCI 2011



Intravenous injection of FGF23 results in LVH in mice.

JCI 2011



Pharmacological inhibition of FGFR attenuates LVH in an animal model of CKD.

JCI 2011

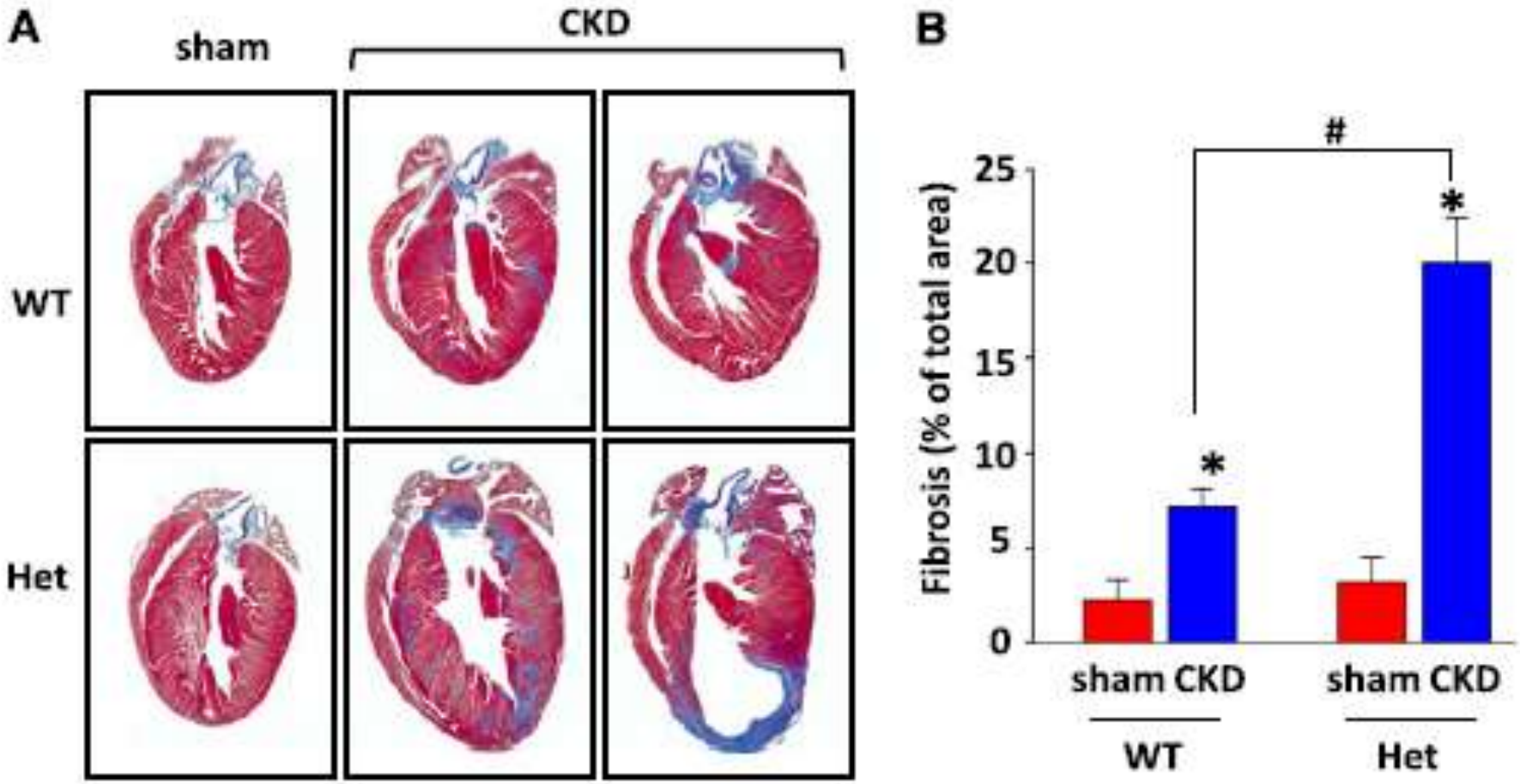
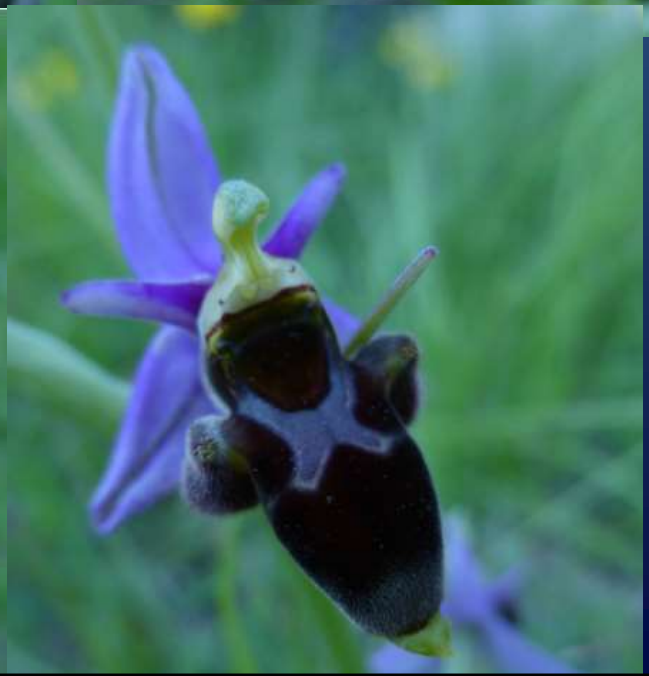


Figure 4. Klotho-deficient CKD mice have aggravated cardiac fibrosis compared with WT mice. (A) Representative trichrome staining of heart sections from WT and Het-*klotho* mice 4 weeks after CKD (shown in duplicate) or sham surgery (shown one time). Blue staining reflects collagen fibers. (B) Mean ±SEM (n 6 per group) of the area of fibrosis relative to the total area of heart sections. *$P<0.05$ versus sham. #$P<0.05$ between indicated groups.



Ophrys scolopax

Ophrys bécasse

Ceçi n’est pas une abeille.

Mortality risk among hemodialysis patients receiving different vitamin D analogs

Table 3 | Hazard ratios (95% confidence intervals) for all-cause mortality for patients who did not receive any vitamin D compared to those who received any type of vitamin D analogue

Model	Covariates	Hazard ratios (95% CI)
1	Unadjusted[a]	1.53 (1.43, 1.63)[b]
2	Age, gender, race, cause of ESRD, and year started HD[a]	1.28 (1.20, 1.37)[b]
3	Model 2 plus baseline calcium, phosphorus, PTH, albumin, *Kt/V*, creatinine, and Hct[c,d]	1.21 (1.10, 1.33)[b]
4	Model 3 plus clinic SMR[e]	1.20 (1.10, 1.32)[b]

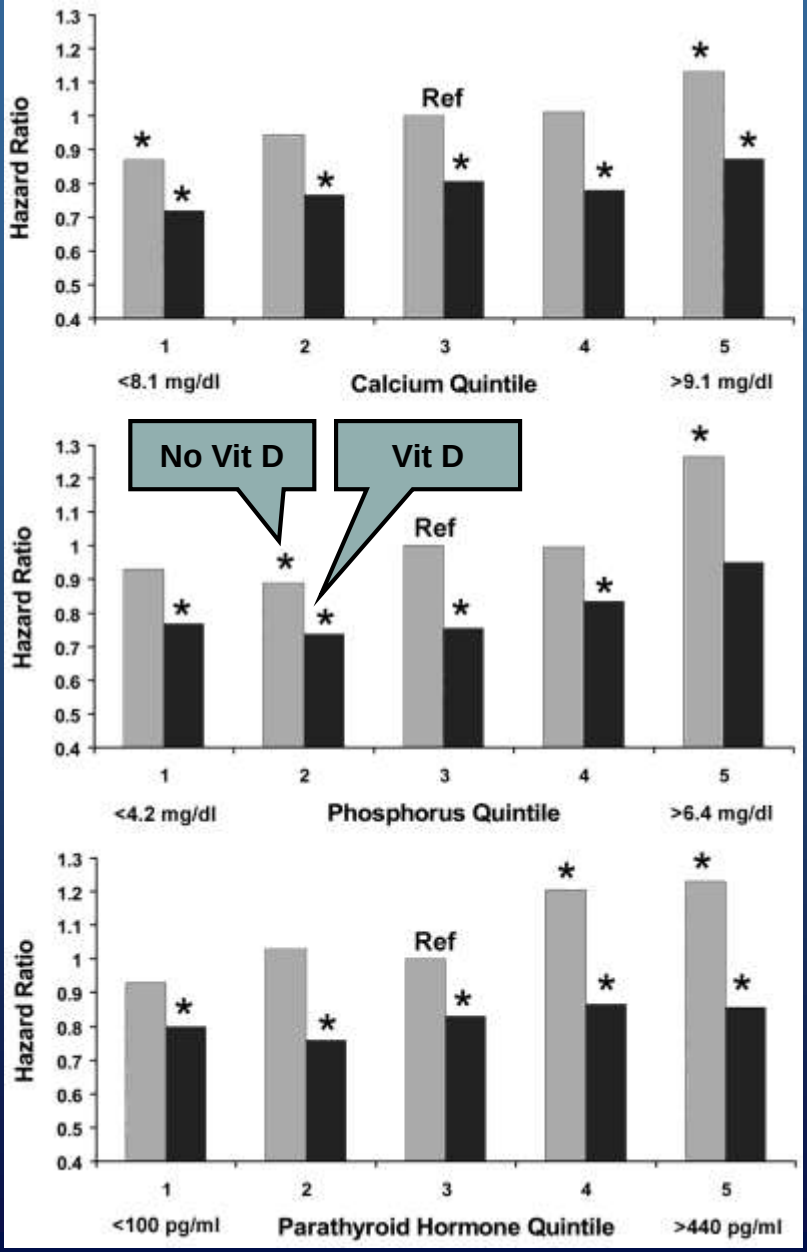
CI, confidence interval; ESRD, end-stage renal disease; Hct, hematocrit; HD, hemodialysis; PTH, parathyroid hormone; SMR, standardized mortality.
[a]Patients, n=14 967; deaths, n=4238.
[b]$P<0.05$.
[c]Patients, n=9355; deaths, n=2725.
[d]Baseline laboratory over the first 30 days on HD.
[e]Patients, n=9351; deaths, n=2723.

In all models mortality was higher for patients who did not receive vitamin D vs. those who did (1.2 (1.1-1.3))

Tentori F et al, Kidney Int 70: 1858-1865, 2006

DDW3569

Activated injectable vitamin D and hemodialysis survival:
A historical cohort study

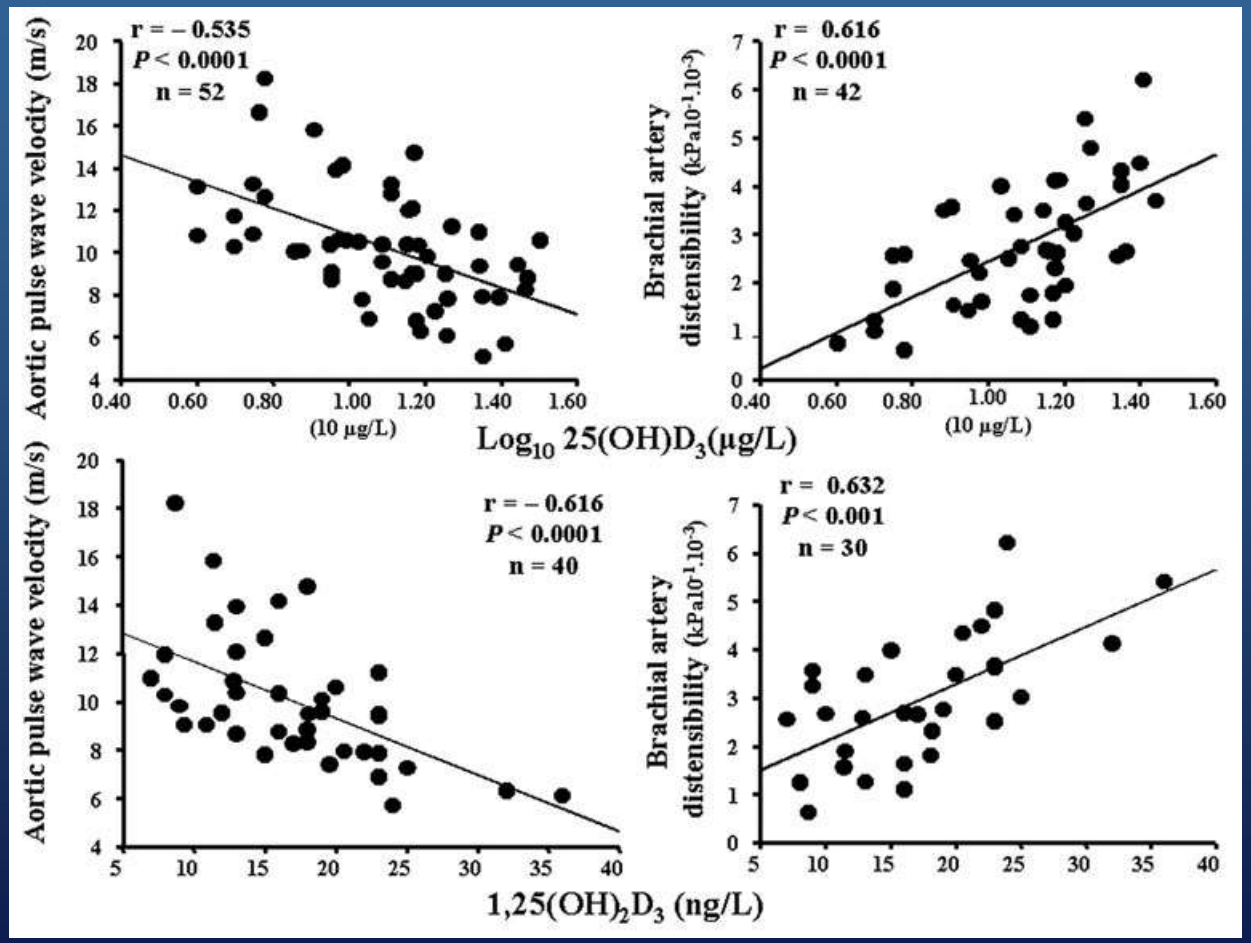


Teng M et al, J Am Soc Nephrol 16: 1115-1125, 2005

DDW3569

Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency

CUSHIONING FUNCTION
dampen blood flow pressure oscillations

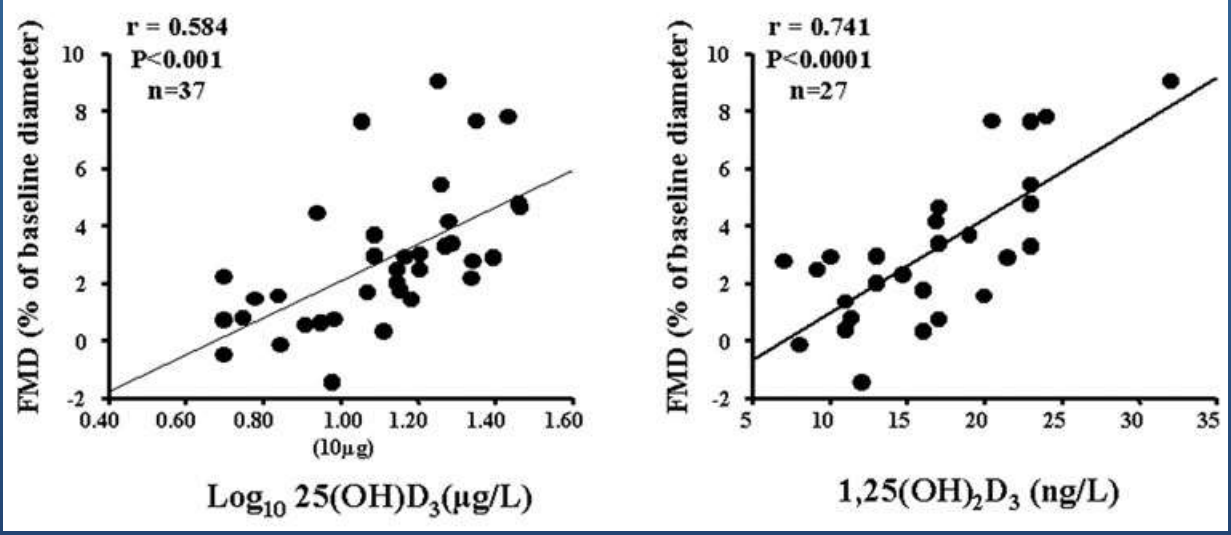


London GM et al, JASN 18: 613-620, 2007

DDW3569

Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency

CONDUIT FUNCTION
blood supply from heart to peripheral tissue



Limitations:

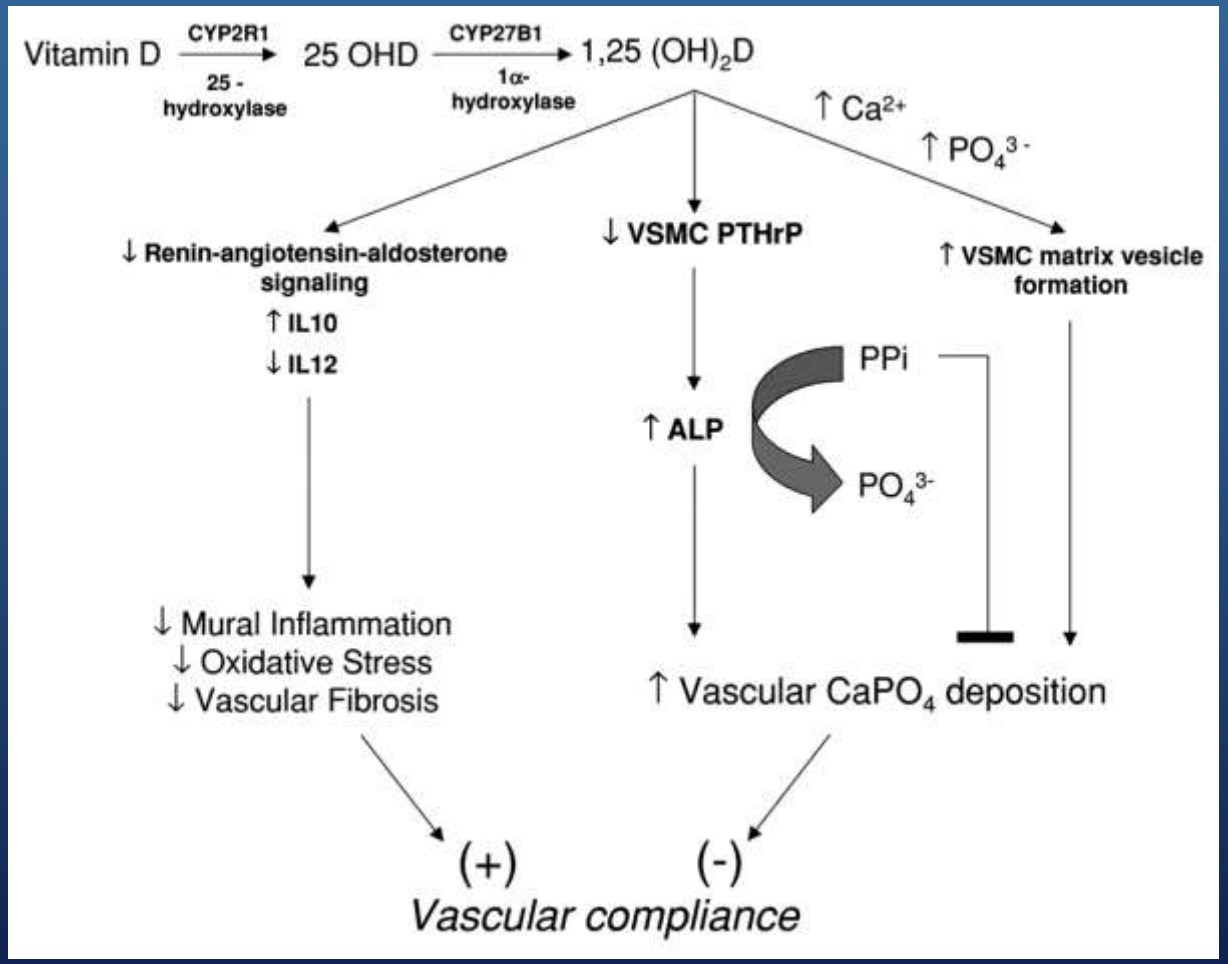
- Patients were clinically stable with normal lipid status, no malnutrition, no inflammation
- Non-supplemented vitamin D deficient patients
- Observational nature of the study – hypothesis generating

London GM et al, JASN 18: 613-620, 2007

FMD flow mediated dilation

DDW3569

Calciotropic hormones and arterial physiology:
"D"-lightful insights



Working model outlining of biphasic actions of vitamin D on vascular compliance

Need for beter 'vit D' analogs

Towler DA: JASN 18: 369-373, 2007

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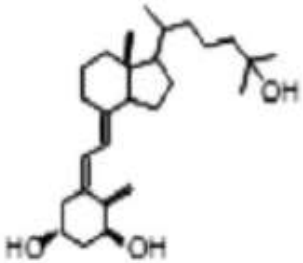
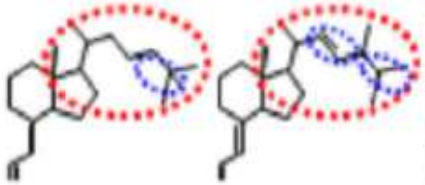
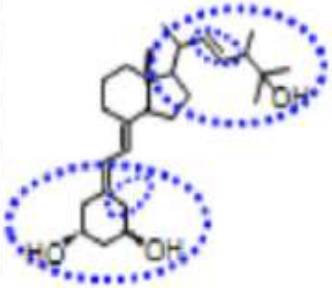
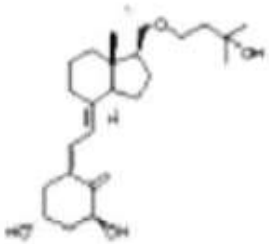
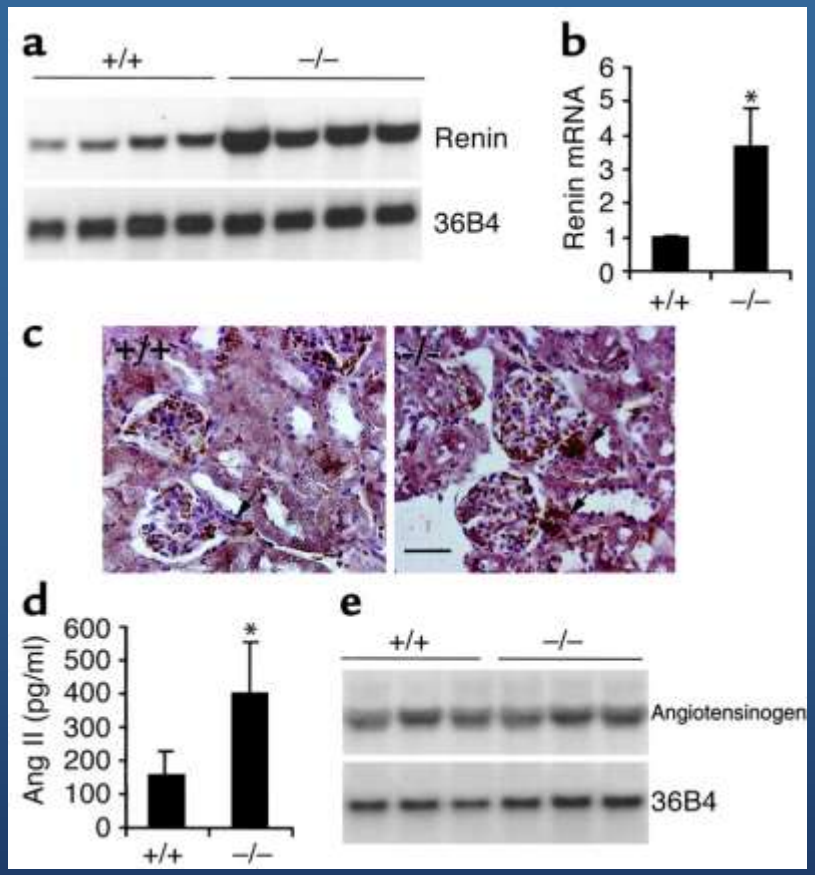
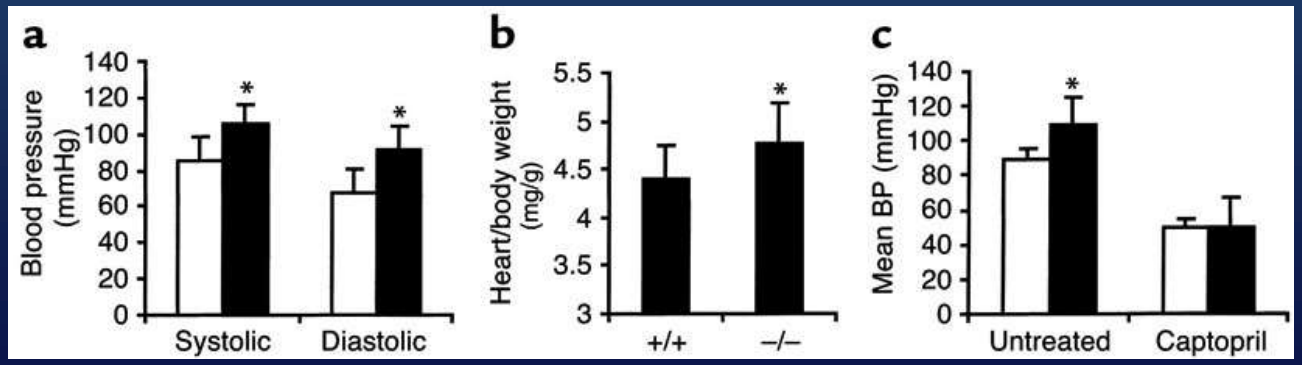
Non-selective VDRA		Selective VDRA (D-mimetics)	
1st Generation	2nd Generation	3rd Generation	
	 Pro Hormones Hepatic Activation		
Calcitriol 1α,25-dihydroxyvitamin D_3	**Alfacalcidol (D3)** **Doxercalciferol (D2)** 1α-hydroxyvitamin D_3/D_2	**Paricalcitol** 19-nor-1α,25-dihydroxyvitamin D_2	**Maxaalcitol** 22-oxa-1,25-dihydroxyvitamin D3
Mimics endogenous VDR hormone	Molecular modifications at the side-chain	Molecular modifications at the side-chain and A-ring	Molecular modifications
Generics (IV& Oral)	**Alpha D3** ® Hectorol®	**Zemplar®**	**Oxarol®**
Osteoporosis, Hypocalcemia	sHPT in CKD Osteoporosis, Hypocalcemia	sHPT in CKD (Stages 3, 4, 5)	sHPT in CKD

1,25-Dihydroxyvitamin D3 is a negative endocrine regulator of the renin-angiotensin system

Effect of VDR inactivation on renin expression and plasma Ang II production



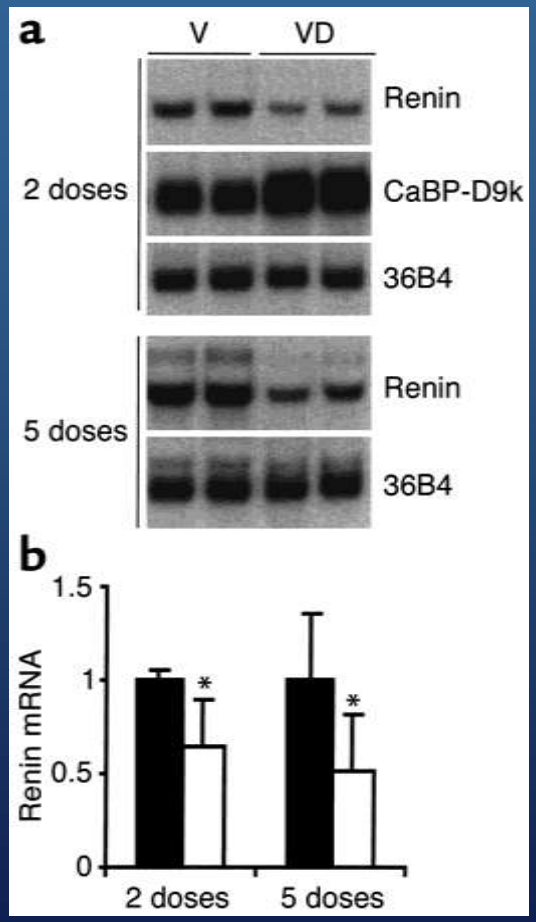
Effect of VDR inactivation on blood pressure and heart weight/body weight ratio

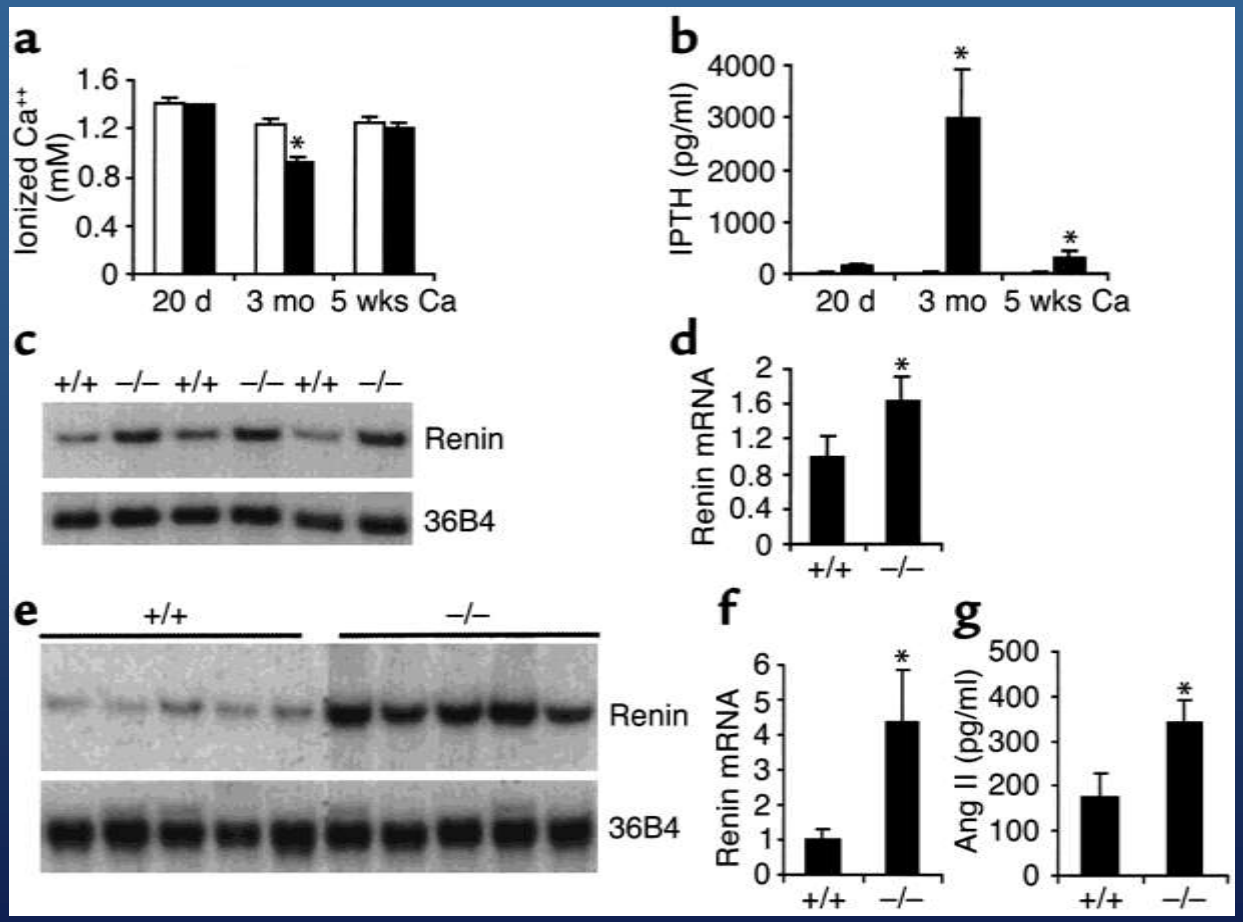


Li YC et al: JCI 110: 229-238, 2002

DDW3566

1,25-Dihydroxyvitamin D3 is a negative endocrine regulator of the renin-angiotensin system





1,25-Dihydoxyvitamin D3 suppresses renin expression in wild-type mice

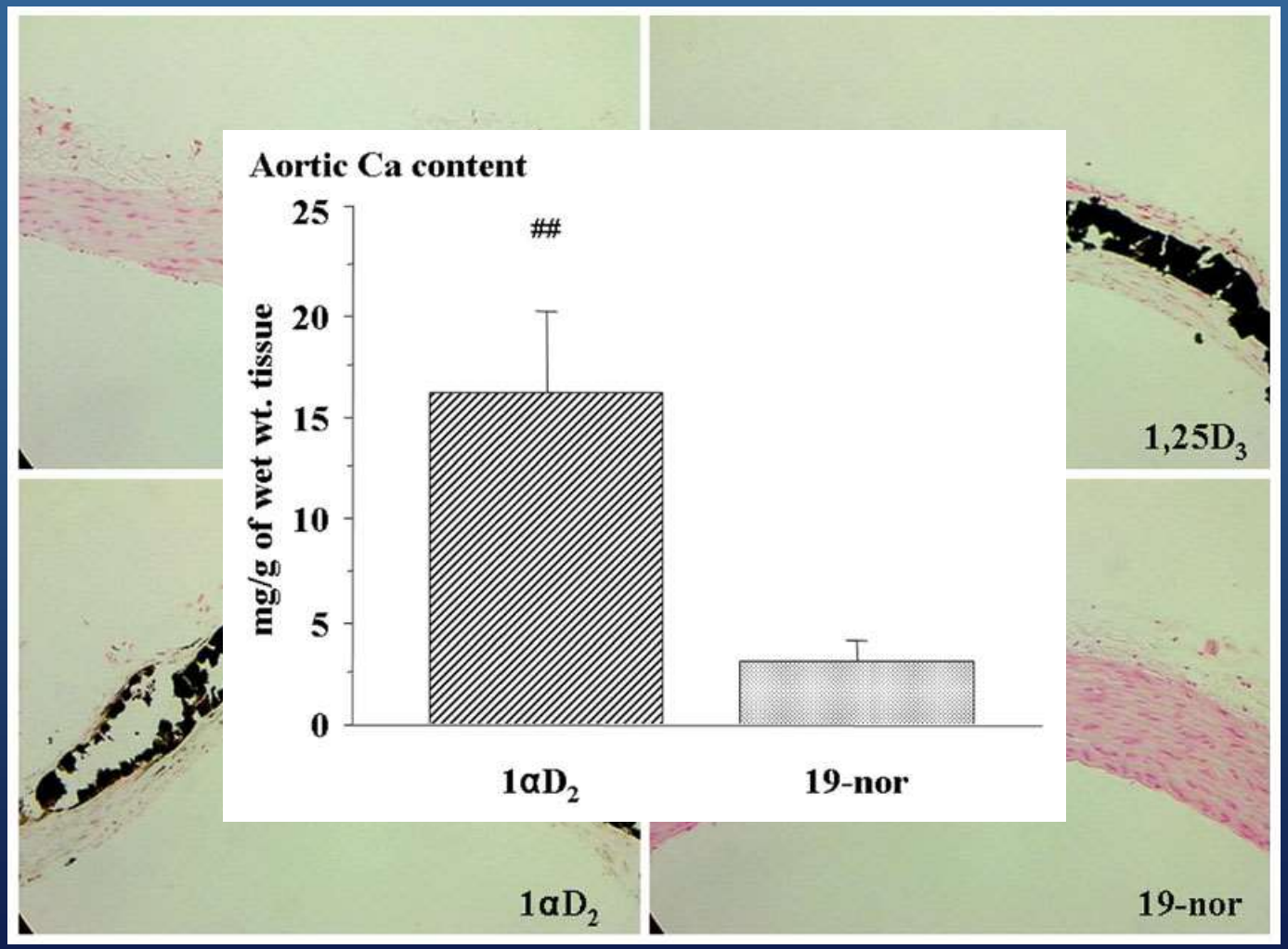
Renin upregulation is independent of the calcium status

Li YC et al: JCI 110: 229-238, 2002

DDW3566

Differential effects of vitamin D receptor activators on vascular calcification in uremic rats

19-nor
paricalcitol



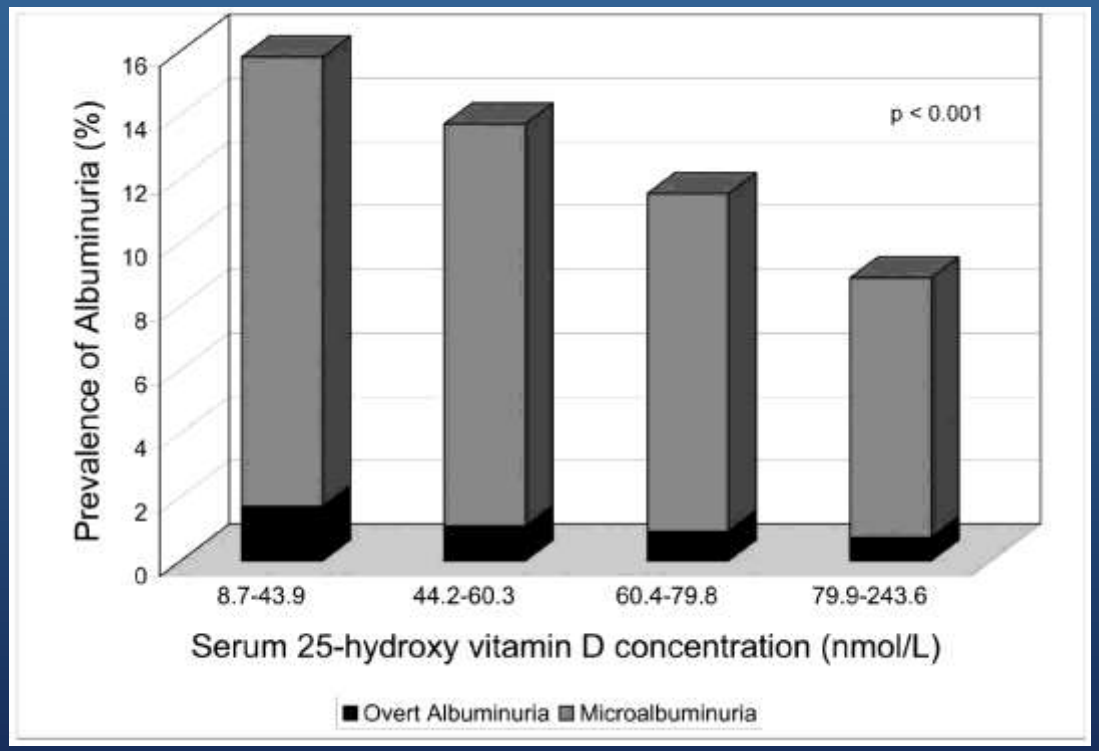
Aorta from uremic rats (Von Kossa staining)

##P < 0.01 versus 19-nor
by non-paired t test

Mizobuchi M et al: Kidney Int: in press 2007

DDW3607

Low serum 25-hydroxy vitamin D levels are associated with albuminuria



Unadjusted prevalence of albuminuria by quartile of 25-hydroxy vitamin D concentration.

De Boer et al 2007

Agarwall et al: Antiproteinuric effect of oral paricalcitol in CKD
Kidn Intern 68, 2823 –2828 ,2005

DDW3569

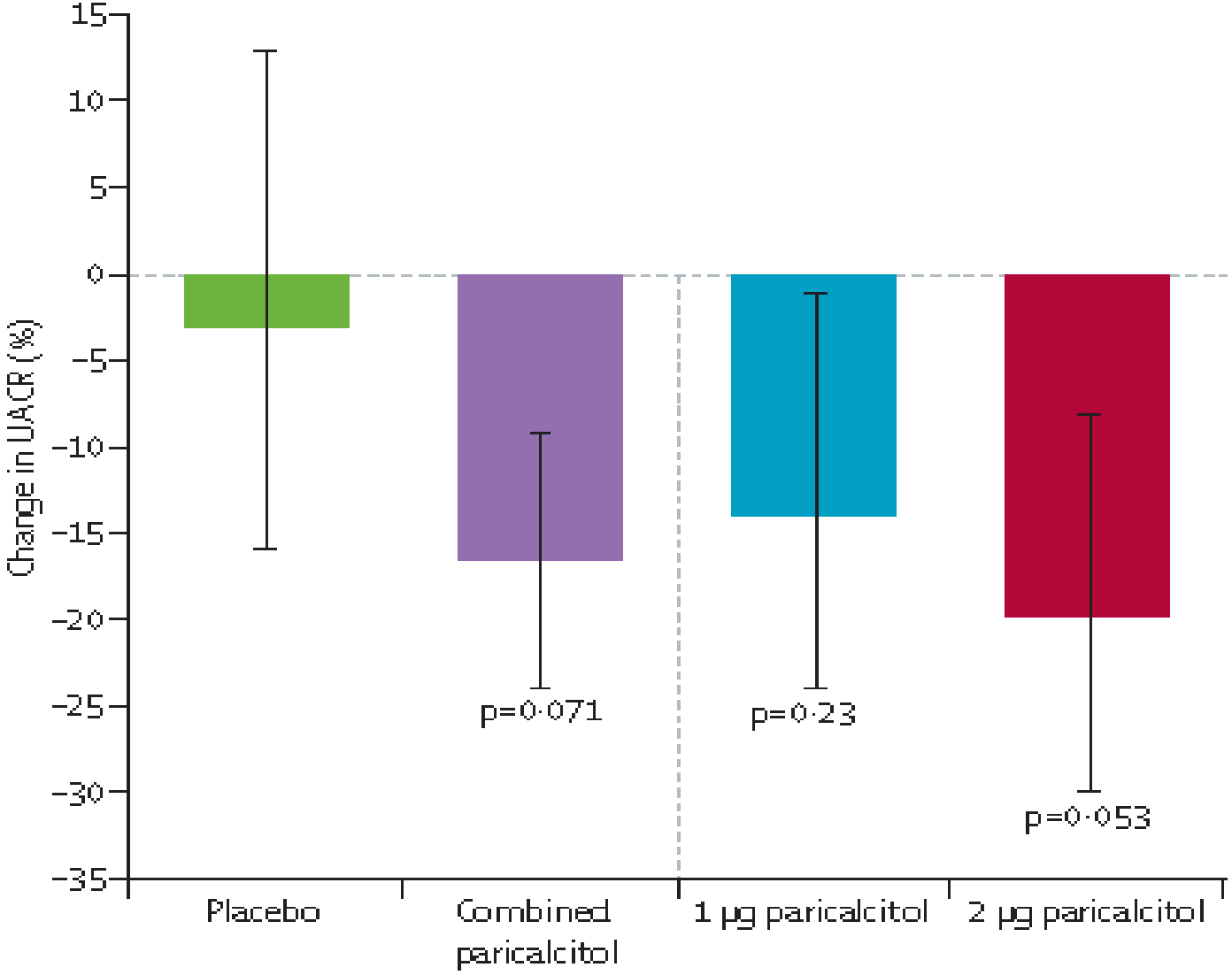
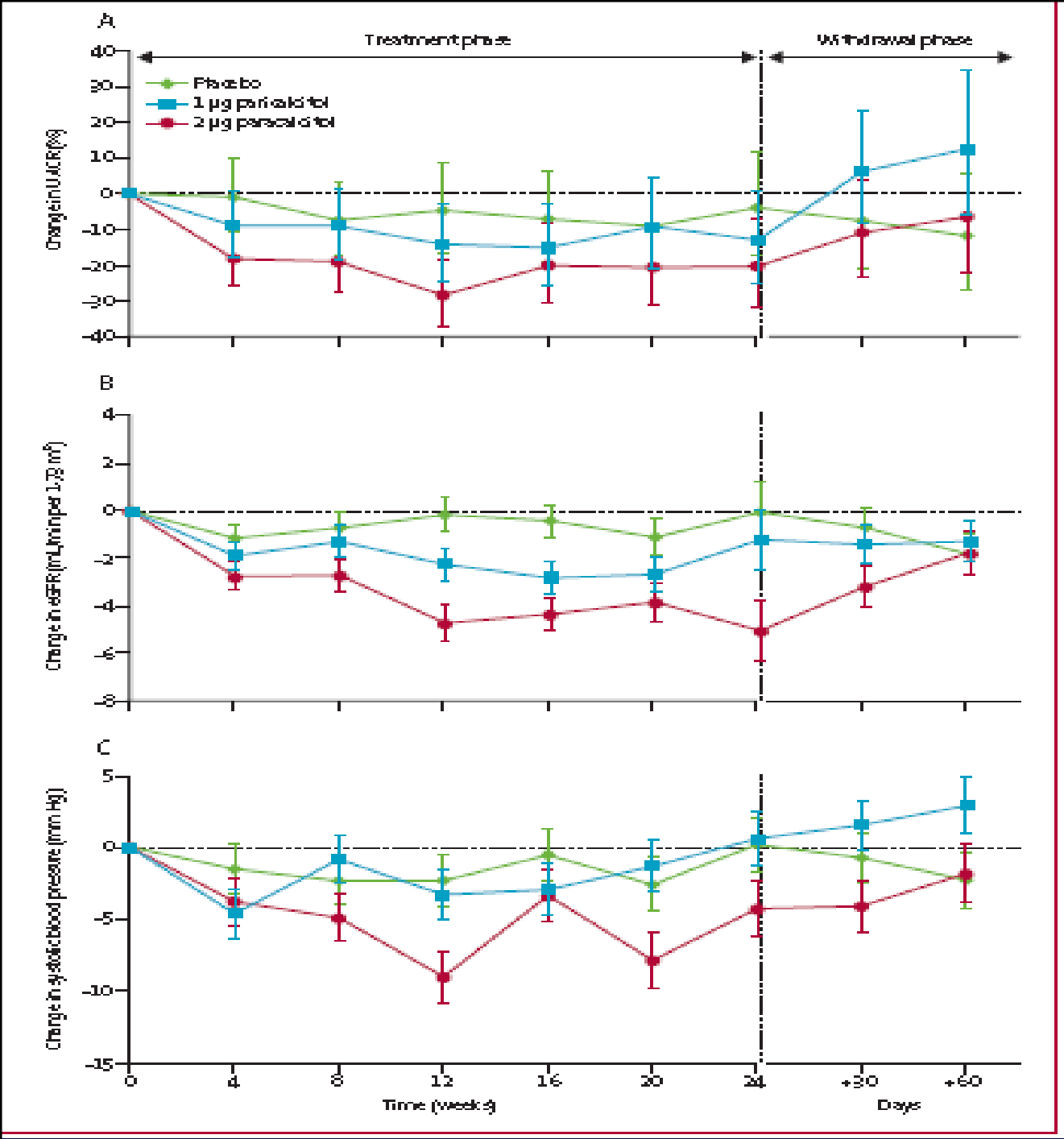


***Figure 2:* Change in urinary albumin-to-creatinine ratio from baseline to the last measurement during treatment**

Error bars represent 95% CIs. p values are for the comparison of paricalcitol versus placebo. UACR=urinary albumin-to-creatinine ratio.

Lancet 2010



Additionally, findings of our study suggest that paricalcitol lowers albuminuria even when dietary sodium intake is high, which is important because resistance to RAAS intervention occurs in people when high dietary sodium intake,

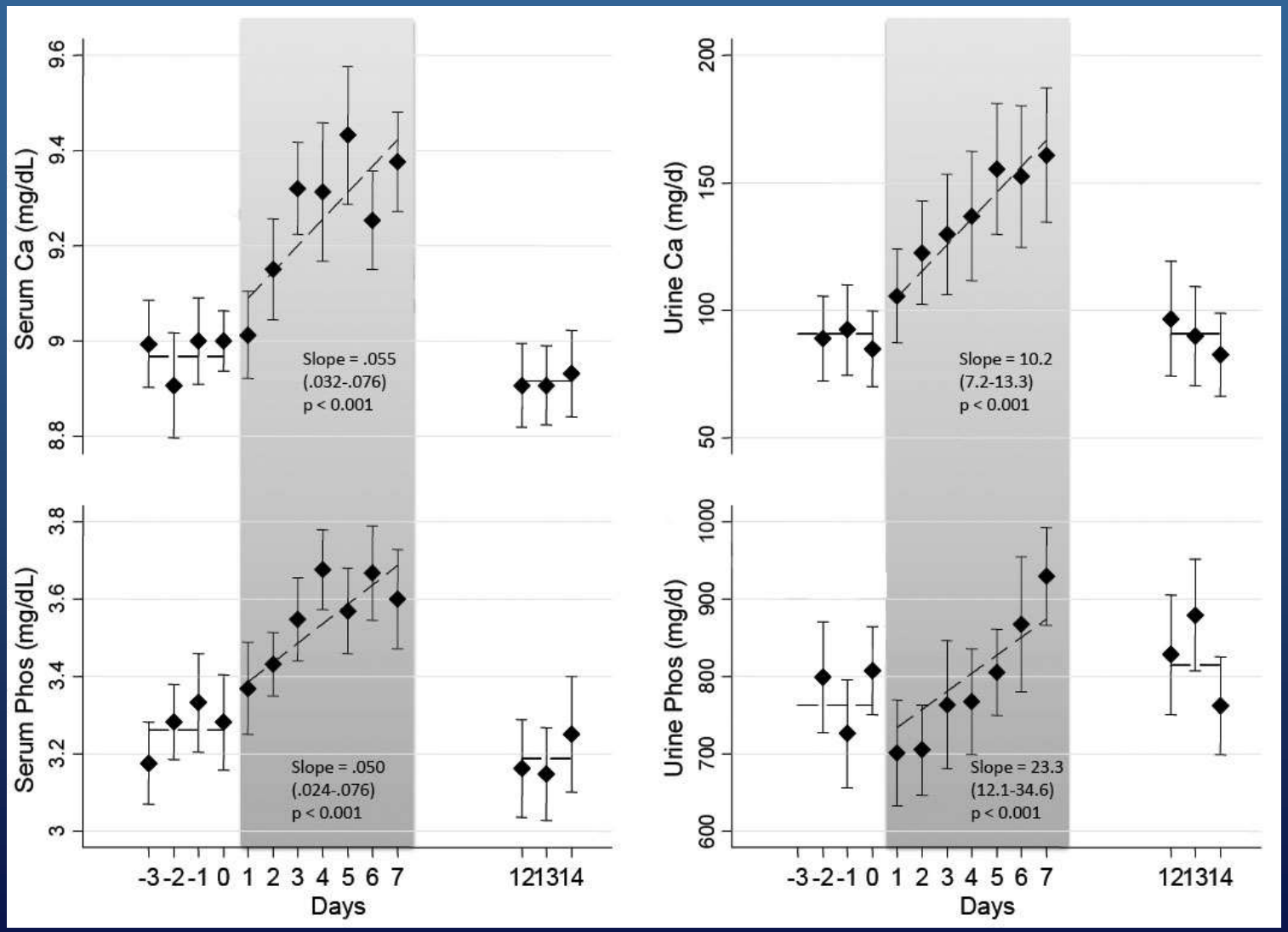
UACR

eGFR

Blood Pressure

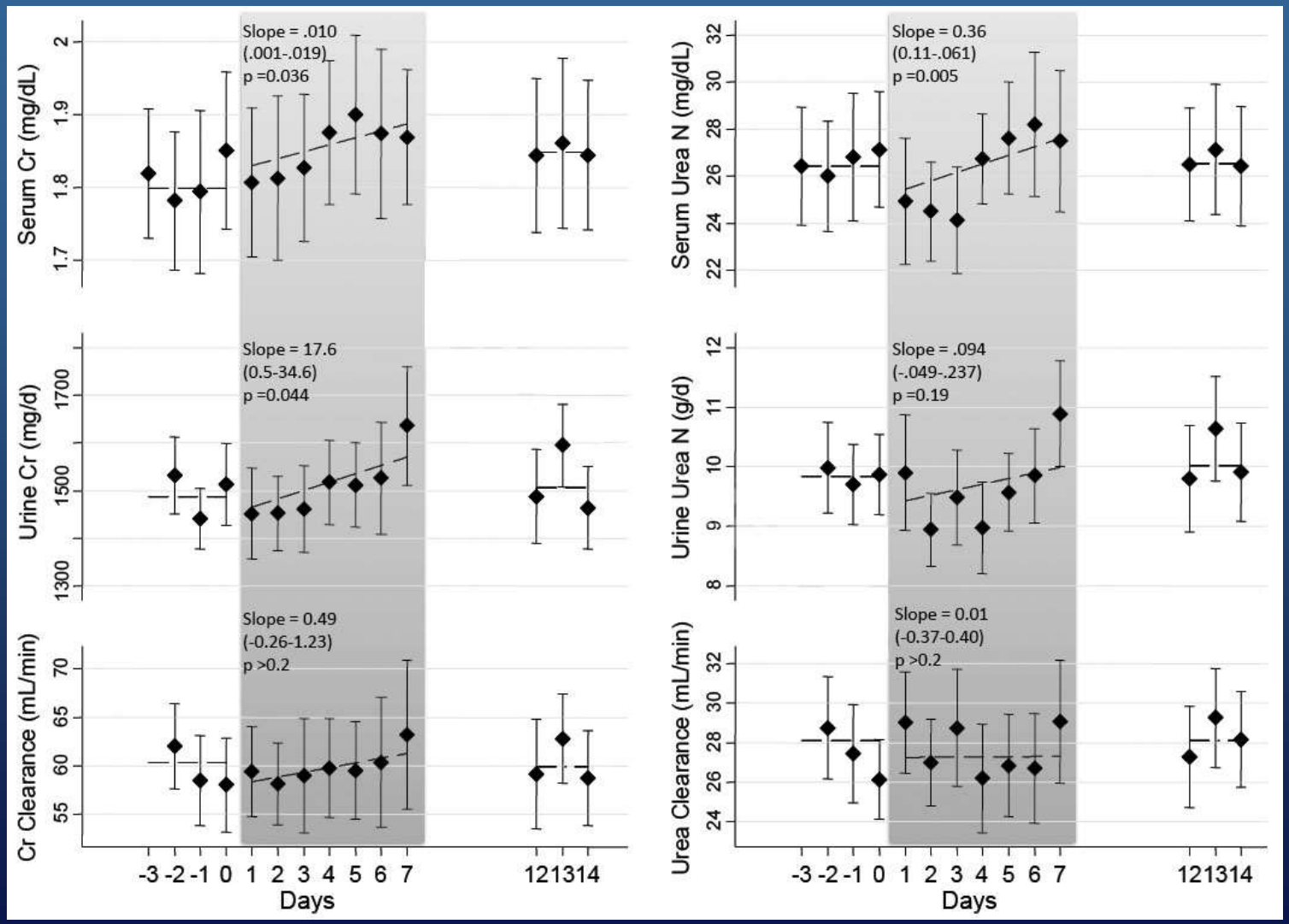
Lancet 2010

Short-term effects of vitamin D receptor activation on serum creatinine, creatinine generation, and glomerular filtration rate



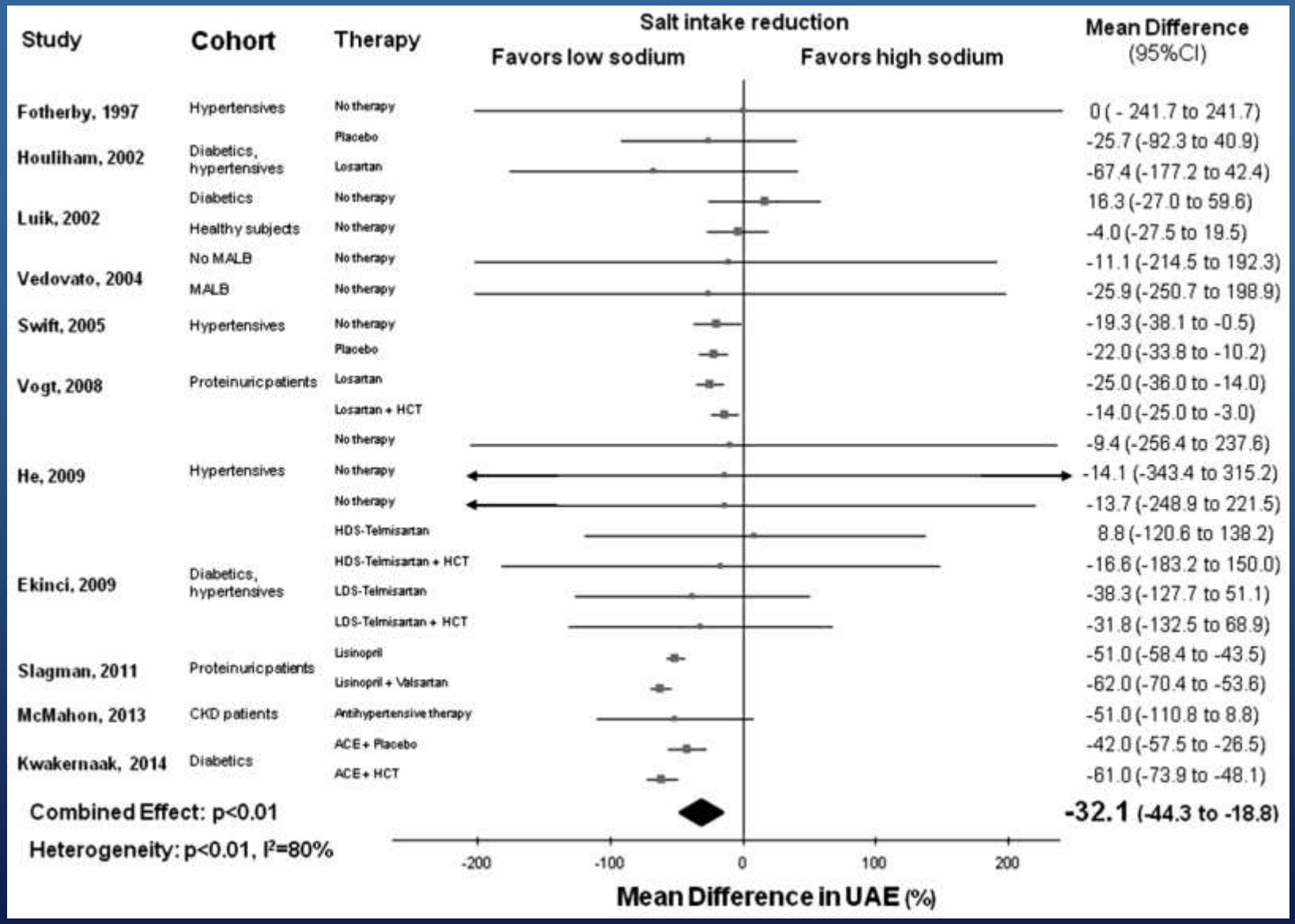
Agarwal R et al: Kidney Int 2011 (In press)

Short-term effects of vitamin D receptor activation on serum creatinine, creatinine generation, and glomerular filtration rate



Agarwal R et al: Kidney Int 2011 (In press)

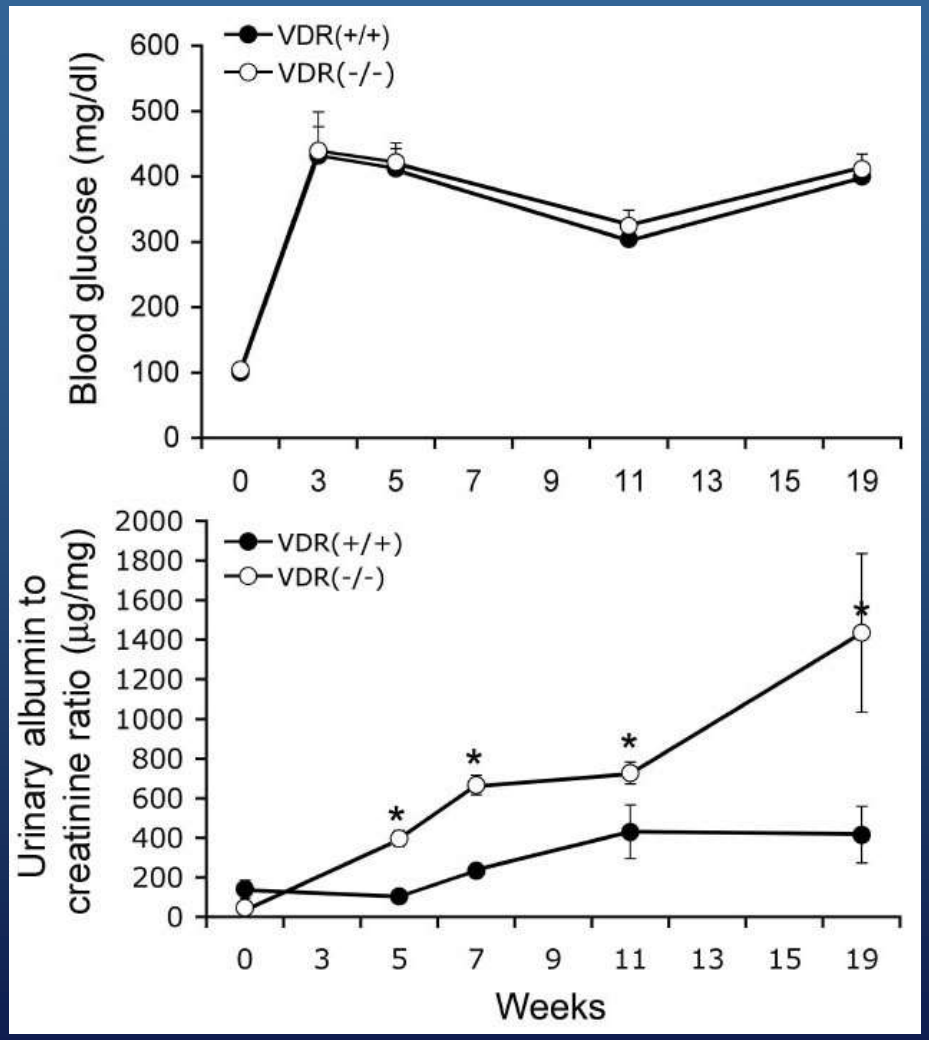
Favorable effect of lower salt consumption on urinary albumin excretion (UAE)



This meta-analysis indicates that sodium intake reduction markedly reduces albumin excretion,more so during concomitant renin-angiotensin-aldosterone system–blocking therapy and amongpatientswith kidney damage.

D'Elia L et al: CJASN 2015, doi:10.2215/CJN.09110914

Renoprotective role of the vitamin D receptor (VDR) in mice with streptozotocin (STZ)-induced diabetic nephropathy



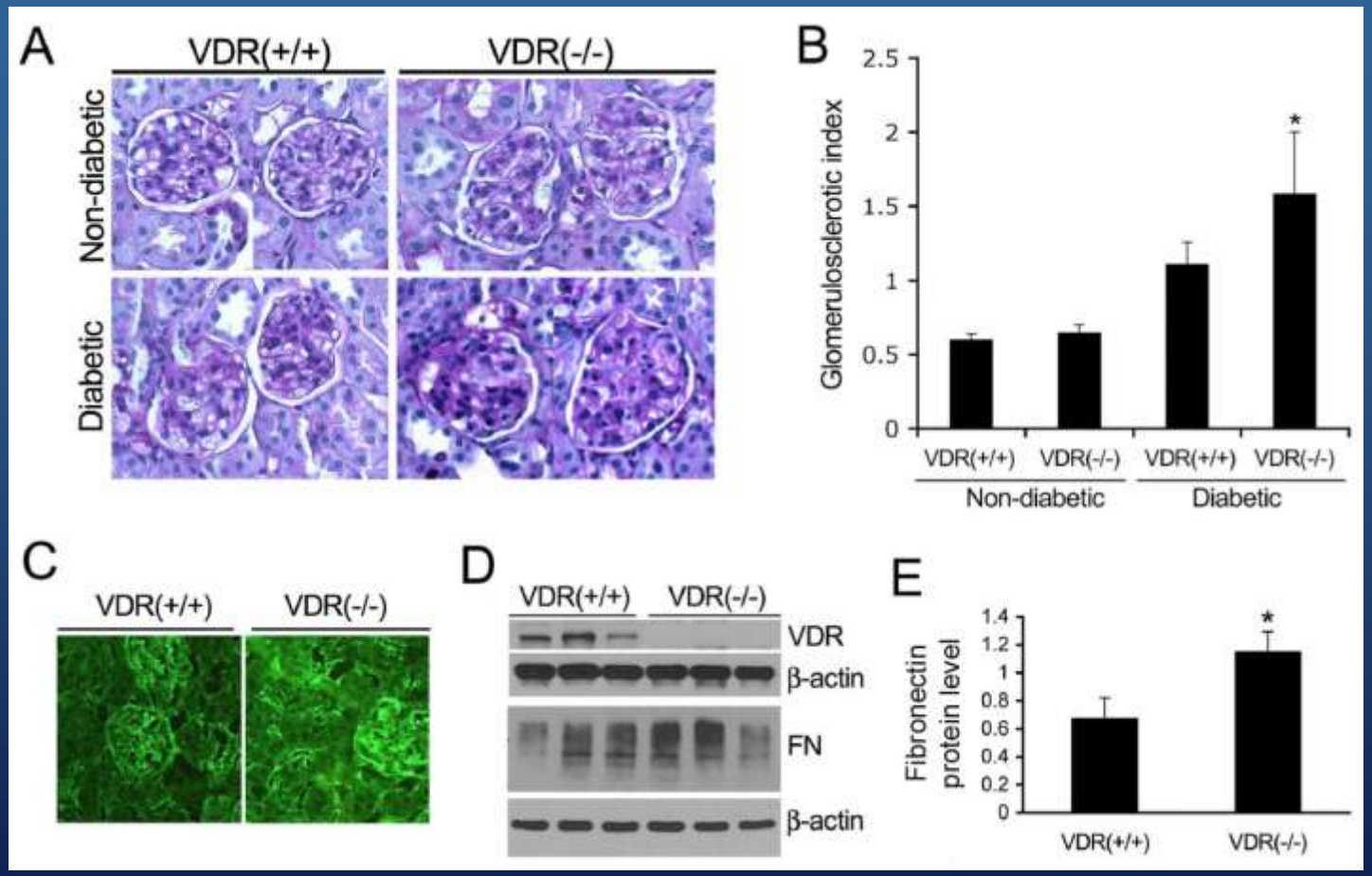
Blood glucose and urinary albumin

* P<0.05 vs. VDR+/+ control, n=5-7 in each genotype.

Zhang Z et al: Kidney Int: in press 2007

DDW3607

Renoprotective role of the vitamin D receptor (VDR) in mice with streptozotocin (STZ)-induced diabetic nephropathy



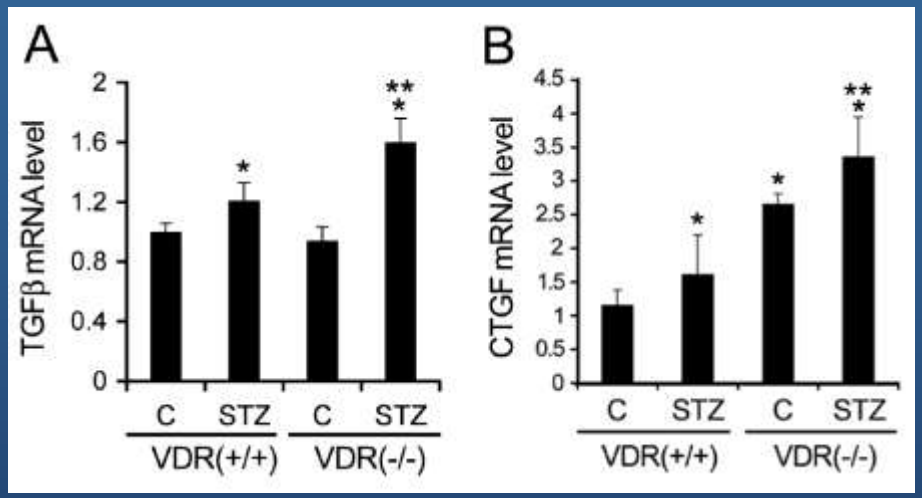
Glomerulosclerosis

* P<0.05 vs. VDR+/+ control, n=3.

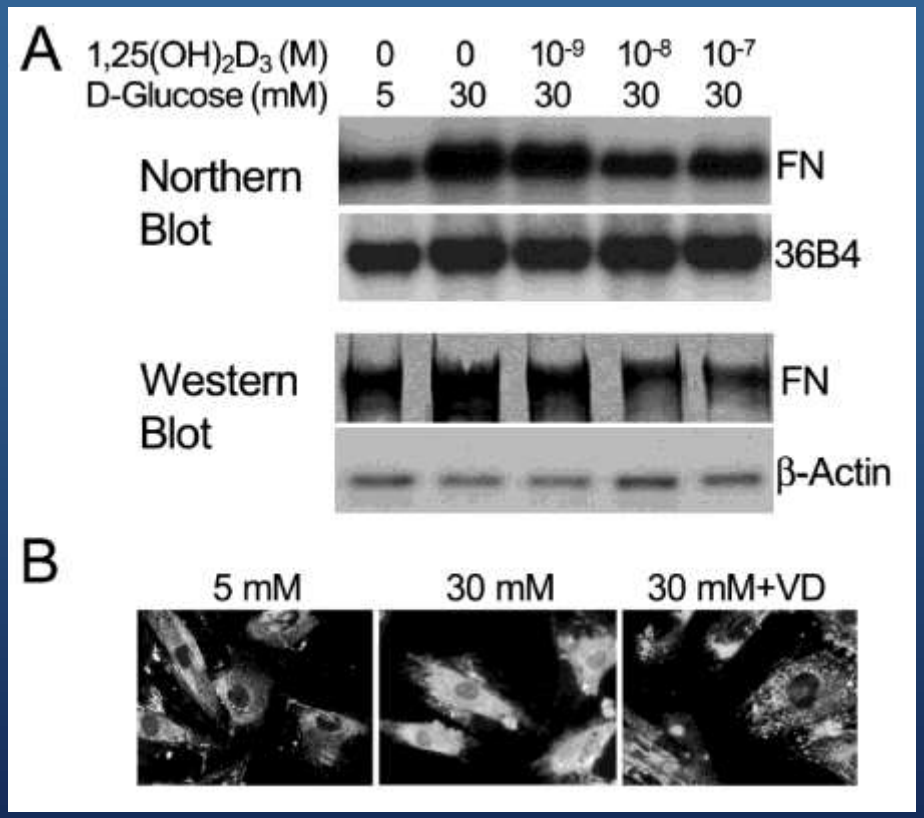
Zhang Z et al: Kidney Int: in press 2007

DDW3607

Renoprotective role of the vitamin D receptor (VDR) in mice with streptozotocin (STZ)-induced diabetic nephropathy



Expression of TGF-β and CTGF in the kidney



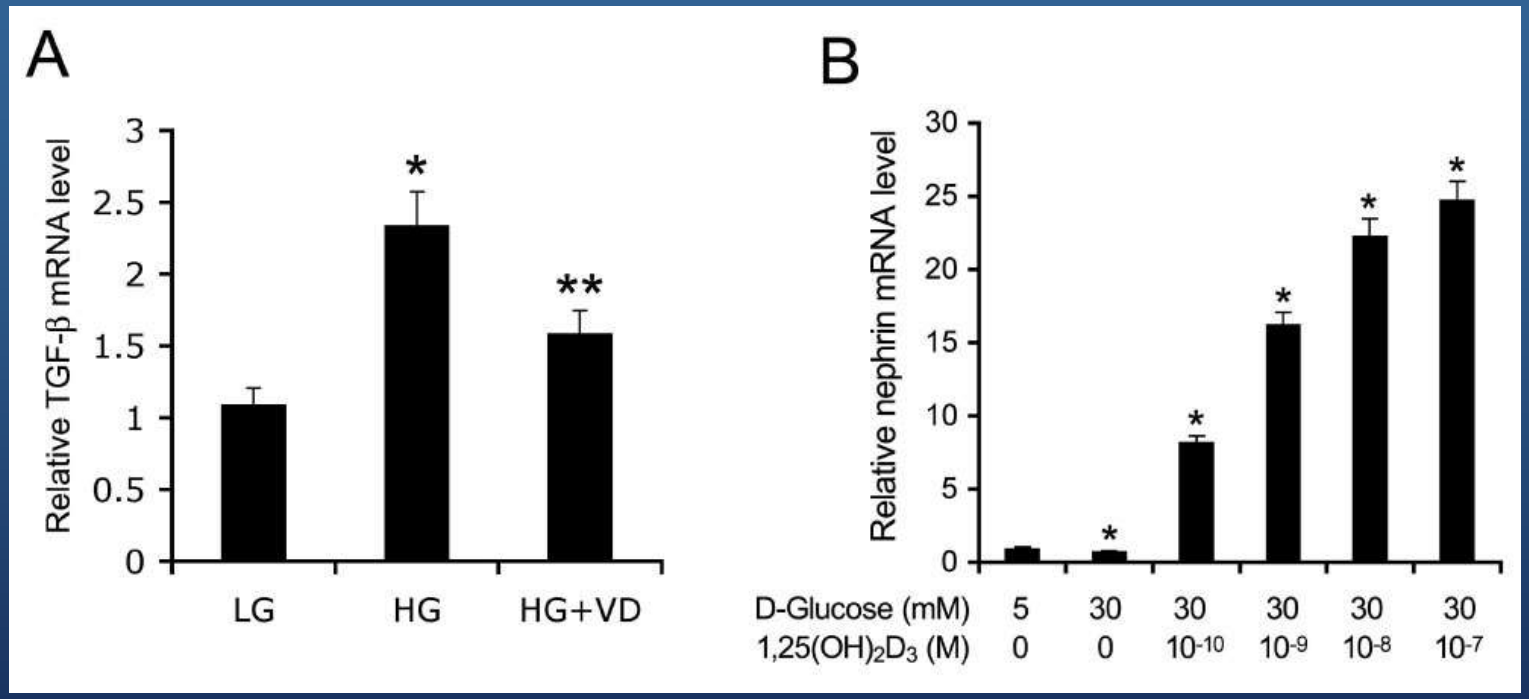
Effect of vitamin D on fibronectin (FN) expression in mesangial cell culture

* P<0.05 vs. VDR+/+ control
** P<0.05 vs. diabetic VDR+/+
n= 4-5

Zhang Z et al: Kidney Int: in press 2007

DDW3607

Renoprotective role of the vitamin D receptor (VDR) in mice with streptozotocin (STZ)-induced diabetic nephropathy



Effect of vitamin D on TGF-β and nephrin expression in cell cultures

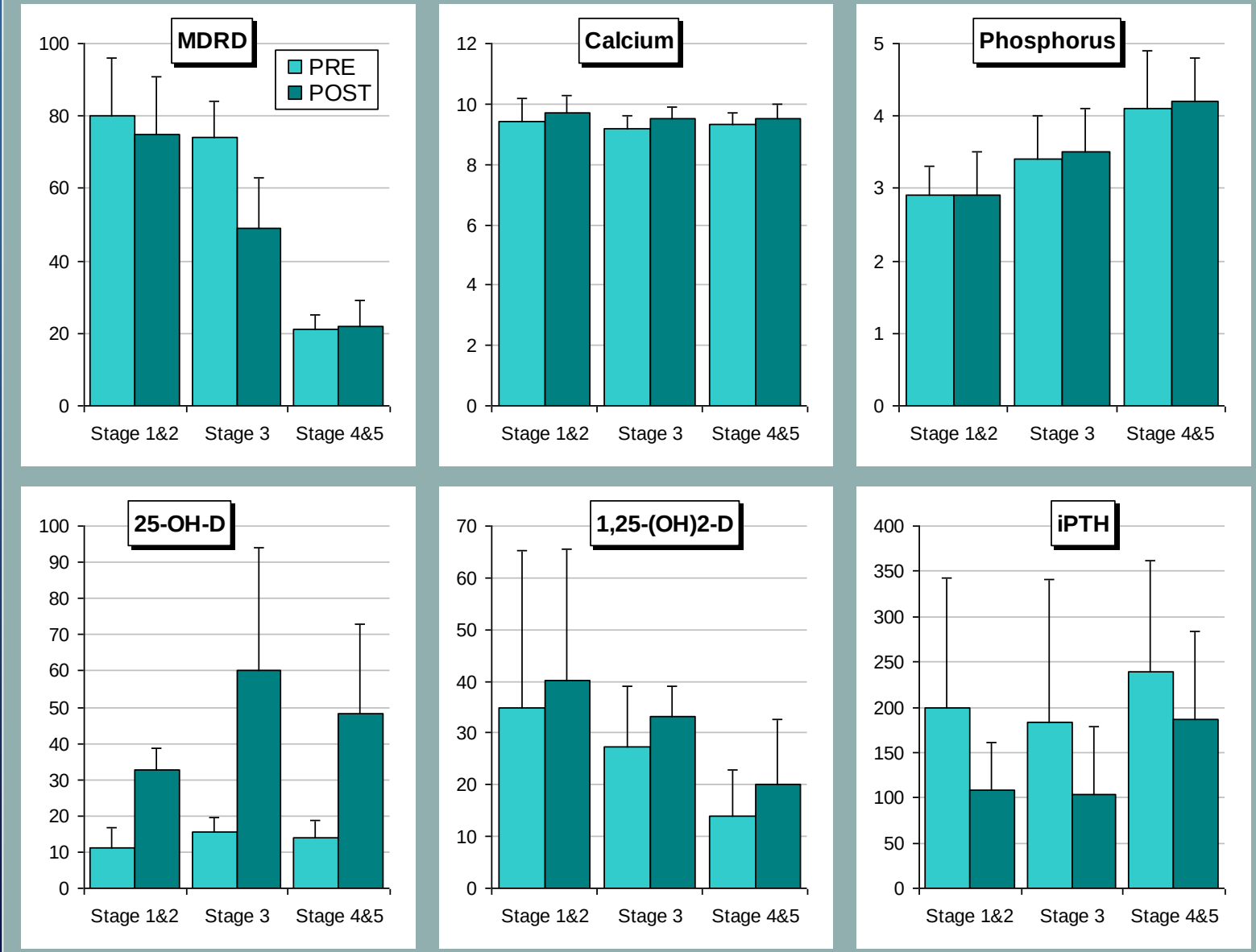
* P<0.05 vs. low glucose (LG)
* P<0.05 vs. high glucose (HG)

Zhang Z et al: Kidney Int: in press 2007

DDW3607

Vitamin D lowers PTH

Ergocalciferol
50,000 IU/week
12 weeks



Chronic kidney disease patients

Finn W, 2007

DDW3569

Meta-analysis: vitamin D compounds in chronic kidney disease

- Purpose: **To determine whether vitamin D therapy improves biochemical markers of mineral metabolism and cardiovascular and mortality outcomes in chronic kidney disease**
- Data Sources: **MEDLINE (January 1966 to July 2007), EMBASE (January 1980 to July 2007), and Cochrane databases were searched without language restriction**

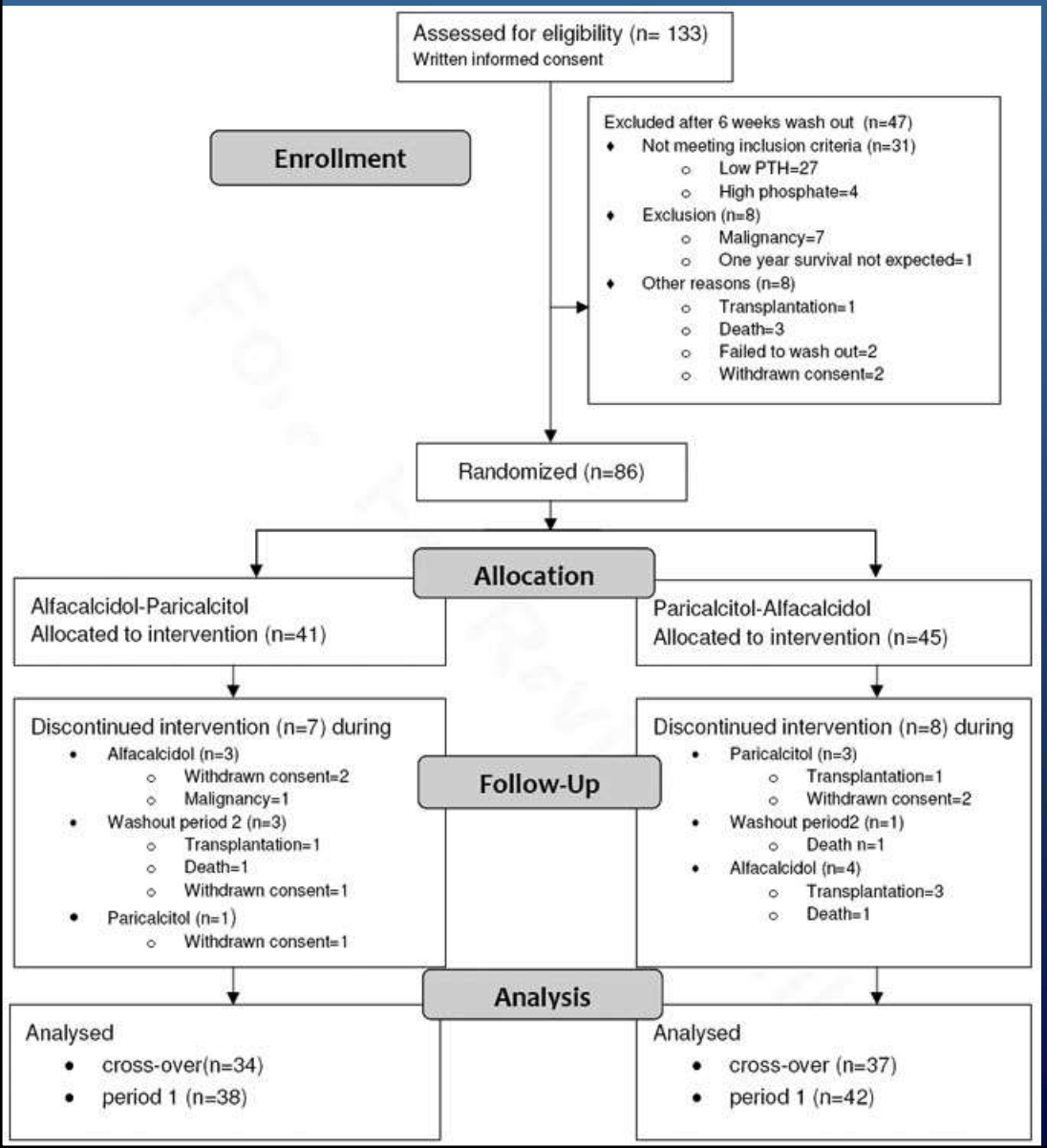
Palmer SC et al: Ann Intern Med 147: 840-853, 2007

Meta-analysis: vitamin D compounds in chronic kidney disease

1. Based on current epidemiologic standards for assessing the validity of interventions, **vitamin D is of unproven efficacy in CKD,** except for its effects on some biochemical indexes
2. Newer vitamin D analogues have **not been shown** to be superior to established vitamin D compounds
3. Intravenous administration is unlikely to be superior to oral dosing
4. Biochemical and experimental data suggest that they may have opposing effects on mortality in this high-risk population, but they have been studied in only around 3000 people, with mortality reported in 8 trials (627 patients)
5. **It is essential for the nephrology community to better address the effects of intervention with these widely used agents on patient-based outcomes**

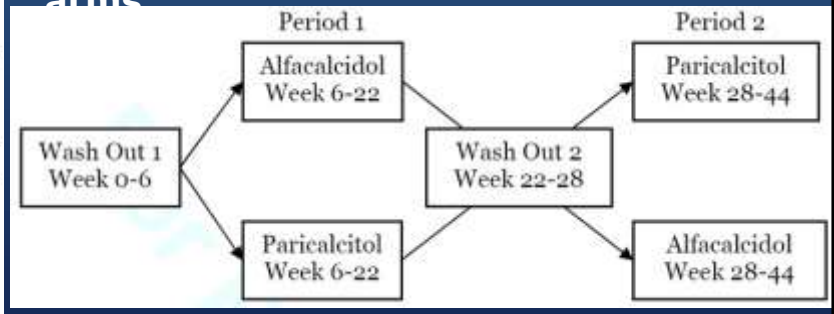
Palmer SC et al: Ann Intern Med 147: 840-853, 2007

Comparison of alfacalcidol and paricalcitol for treatment of secondary hyperparathyroidism in hemodialysis patients.
A randomised cross-over study



Participants flow through the study

Treatment periods and treatment arms



Hansen D et al: Kidney Int 2011

Comparison of alfacalcidol and paricalcitol for treatment of secondary hyperparathyroidism in hemodialysis patients.

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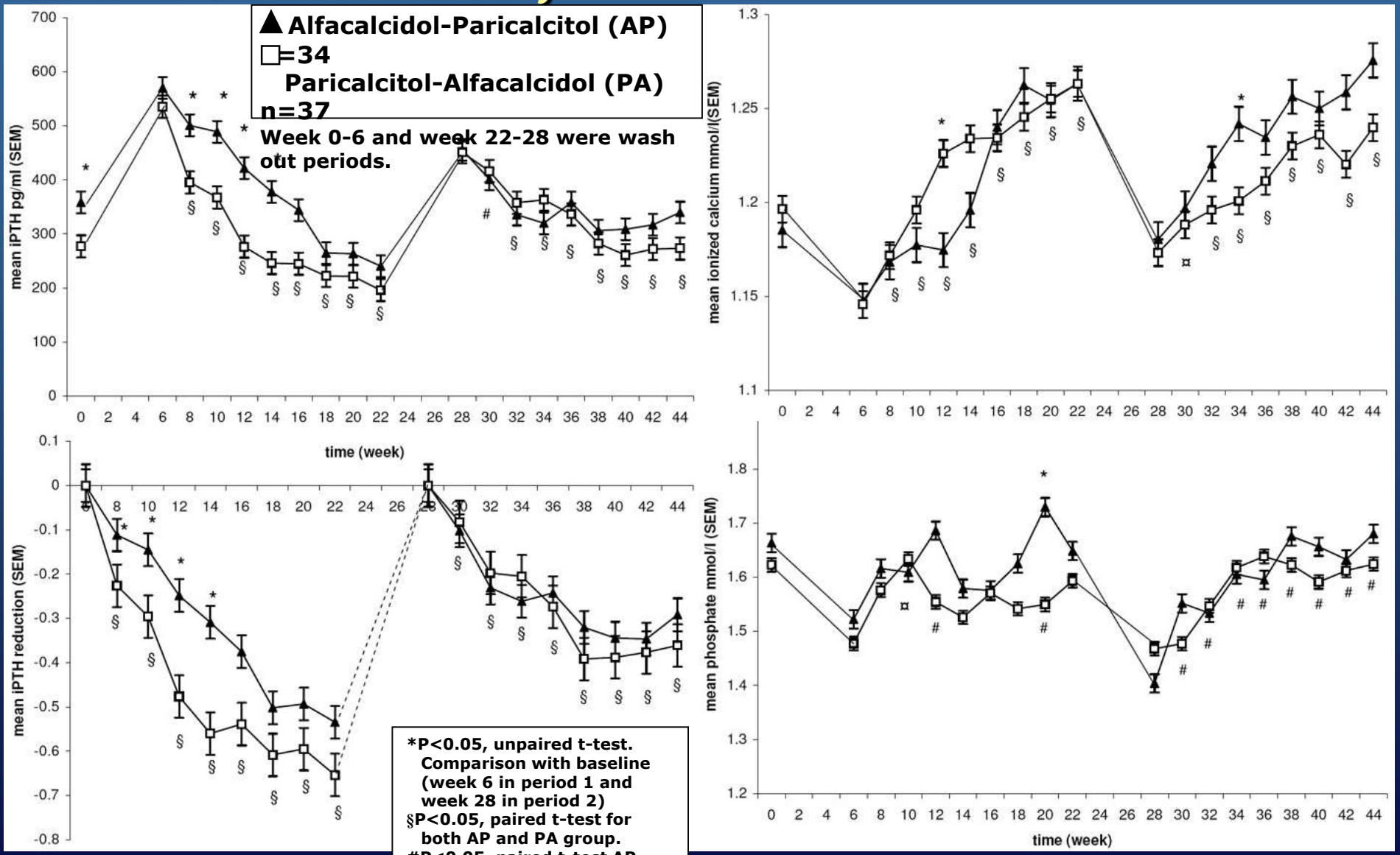


Hansen D et al: Kidney Int 2011

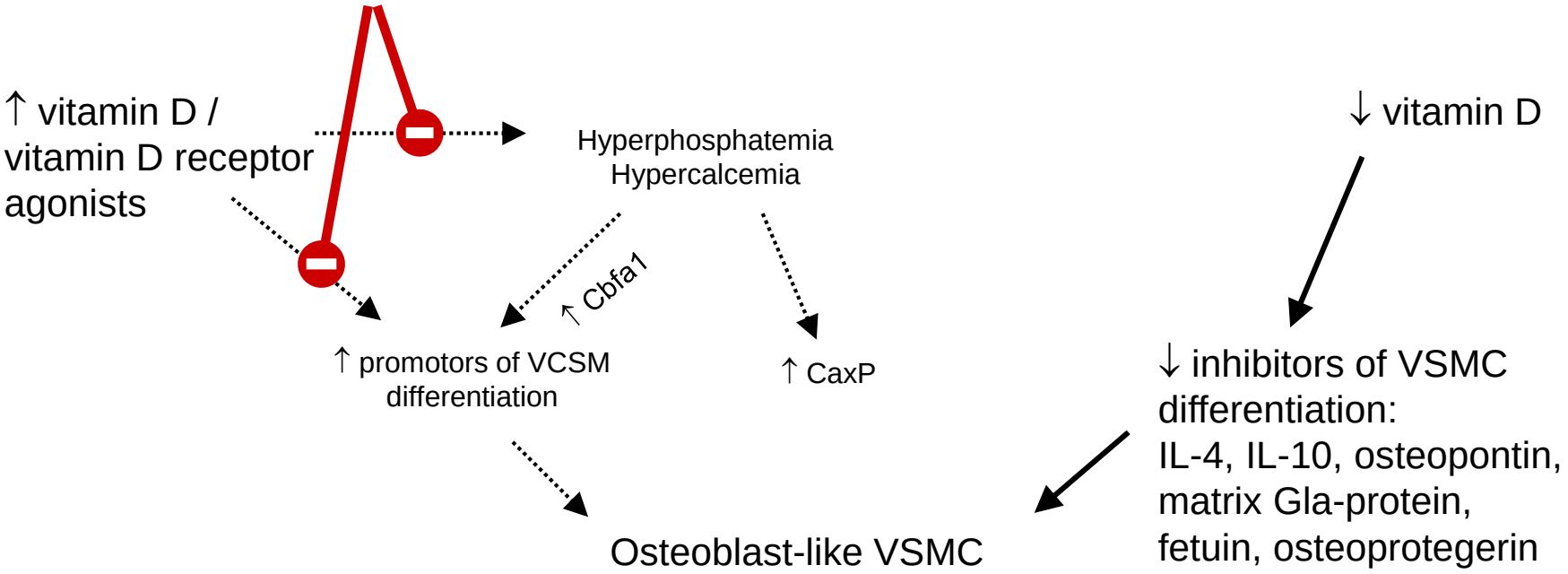
Comparison of alfacalcidol and paricalcitol for treatment of secondary hyperparathyroidism in hemodialysis patients.
A randomised cross-over study

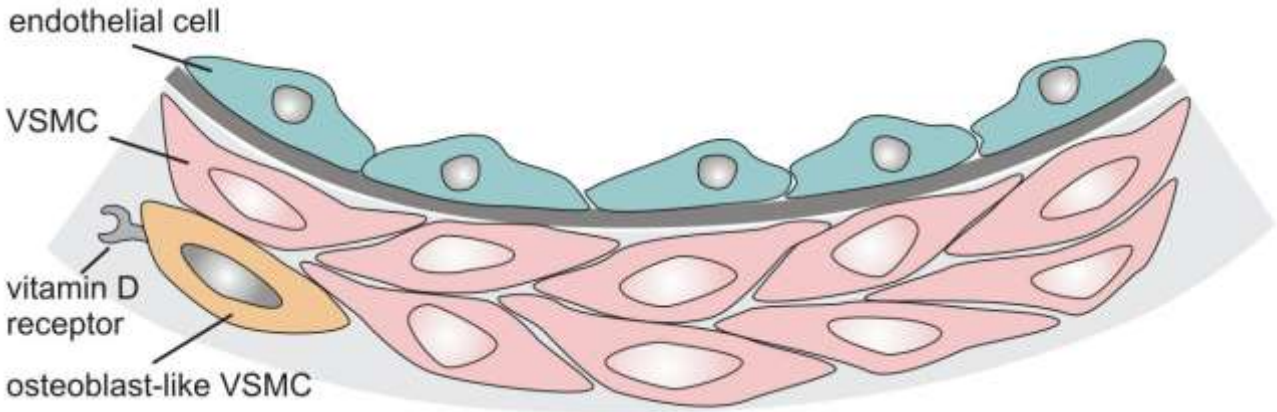
Incidence of hypercalcemia, hyperphosphatemia and elevated Ca x P product.

	Number (%) of patients		
	Alfacalcidol n=38	Paricalcitol n=42	P-value
Hypercalcemia (ionized calcium>1.30 mmol/l) at least once	21 (55%)	24 (57%)	0.866
Hypercalcemia (ionized calcium>1.30 mmol/l) at least two consecutive measurements	12 (32%)	16 (38%)	0.542
Hyperphosphatemia (phosphate≥1.80 mmol/l) at least once	29 (76%)	29 (69%)	0.467
Hyperphosphatemia (phosphate≥1.80 mmol/l) at least two consecutive measurements	17 (45%)	14 (33%)	0.296
Elevated Ca x P ≥ 2.3 $mmol^2/l^2$ at least once	25 (66%)	29 (69%)	0.756
Elevated Ca x P ≥ 2.3 $mmol^2/l^2$ at least two consecutive measurements	14 (37%)	16 (38%)	0.908

Hansen D et al:
Kidney Int 2011

Effect of paricalcitol





Paricalcitol aggravates perivascular fibrosis in rats with RF and low calcitriol

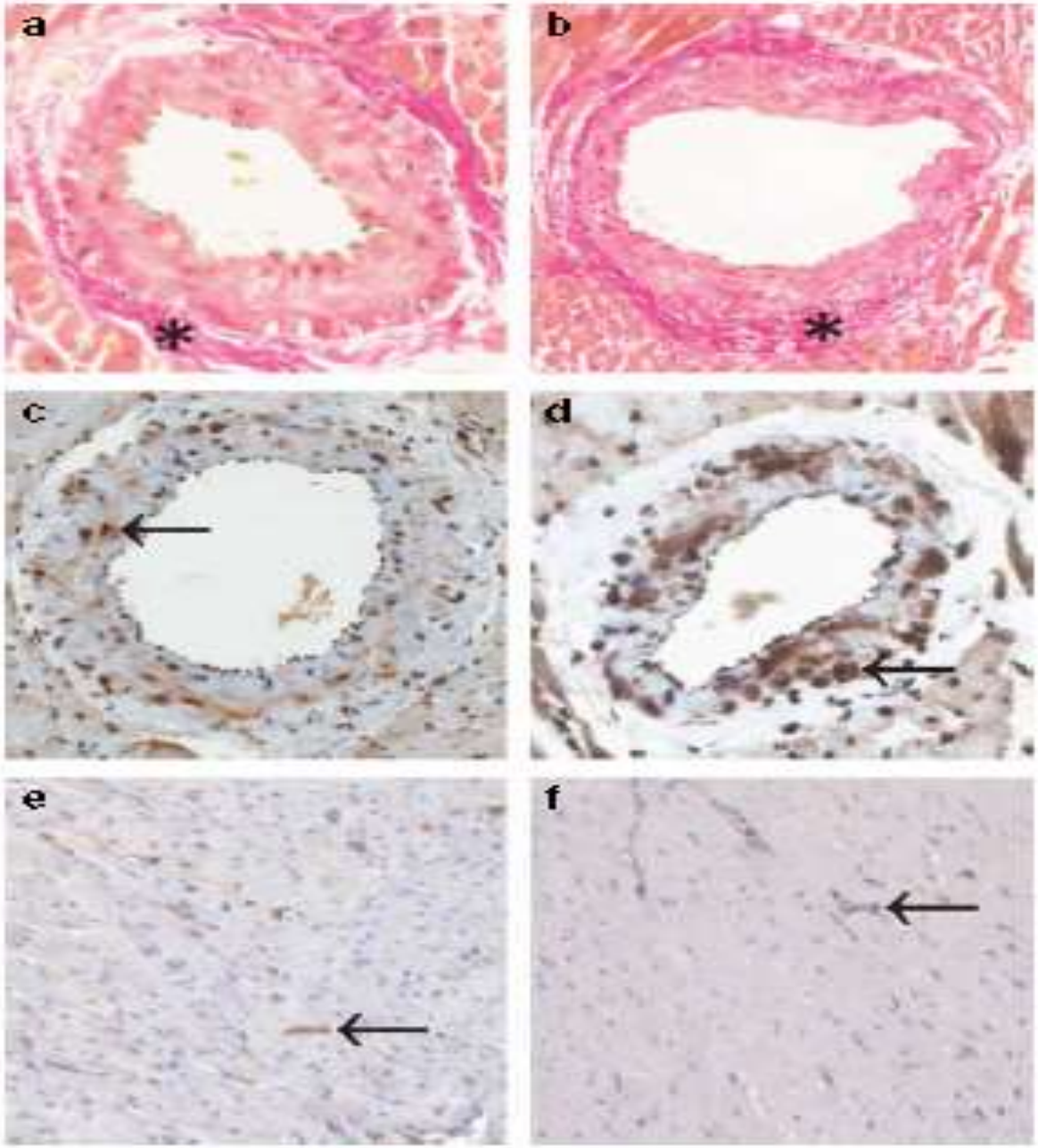


Figure 4 | Cardiac histology. Representative original photomicrographs showing cardiac perivascular fibrosis

Paricalcitol aggravates perivascular fibrosis in rats with renal insufficiency and low calcitriol

JM Repo1, IS Rantala2, TT Honkanen2, JT Mustonen3,4, P Ko¨o¨ bi5, AM Tahvanainen3,4, OJ Niemela¨6,
I Tikkanen7,8, JM Rysa¨9, HJ Ruskoaho9 and IH Po¨ rsti3,4

Kidn Intern. 72; 979 ;2007

Cardiac perivascular fibrosis and connective
tissue growth factor were significantly increased in the remnant kidney groups, and further increased in paricalcitol treated
rats.

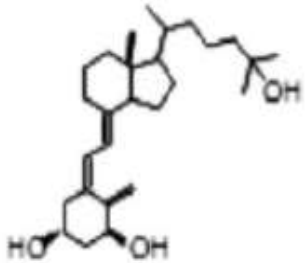
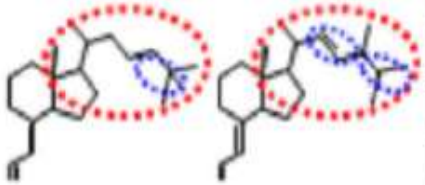
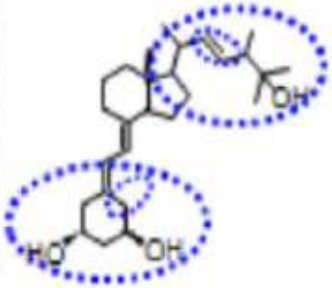
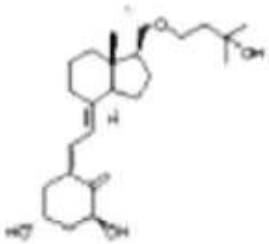
Available Native Vit D

G Jean et al, Néphrologie & Thérapeutique (2009) 5, 520—532

Tableau 1 Les vitamines D natives et le calcifédiol.

Vitamine D	Spécialité	Dosage	Demi-vie	Posologie
Ergocalciférol (vitamine D_2)	Sterogyl®	1 goutte = 400 UI = 10 µg	15—45 j	800—2000 UI/j
	Sterogyl® 15	1 amp = 600 000 UI	15—45 j	1 amp 1—2 × /an
	Uvesterol® D	1 ml = 1500 UI	15—45 j	800—2000 UI/j
Colécalciférol (vitamine D_3)	Zyma D®	1 goutte = 300 UI		600—1800 UI/j
		1 amp = 80 000 et 200 000 UI		80 000 UI/1—2 mois 200 000 UI/3 à 6 mois
	Uvedose®	1 amp 100 000 UI	15—45 j	1 amp/1—2 mois
	Vitamine D3 Bon®	1 amp 200 000 UI	15—45 j	1 amp/2—3 mois
Calcifédiol (25(OH)D_3)	Dedrogyl®	1 goutte = 5 µg	18—21 j	10—5 µg/j

amp : ampoule.

Non-selective VDRA		Selective VDRA (D-mimetics)	
1st Generation	2nd Generation	3rd Generation	
	 Pro Hormones Hepatic Activation		
Calcitriol 1α,25-dihydroxyvitaminD_3	Alfacalcidol (D3) Doxercalciferol (D2) 1α-hydroxyvitamin D_3/D_2	Paricalcitol 19-nor-1α,25-dihydroxyvitamin D_2	Maxaalcitol 22-oxa-1,25-dihydroxyvitamin D3
Mimics endogenous VDR hormone	Molecular modifications at the side-chain	Molecular modifications at the side-chain and A-ring	Molecular modifications
Generics (IV& Oral)	Alpha D3 ® Hectorol®	Zemplar®	Oxarol®
Osteoporosis, Hypocalcemia	sHPT in CKD Osteoporosis, Hypocalcemia	sHPT in CKD (Stages 3, 4, 5)	sHPT in CKD

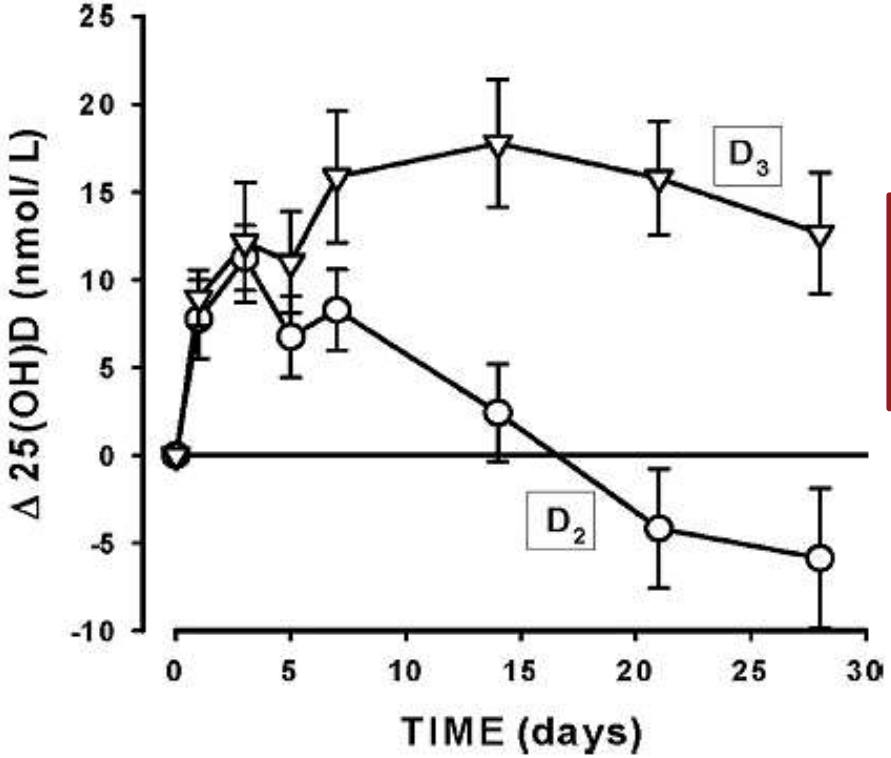
Recommended concentrations

Taux inadéquats : supplémentation nécessaire

25 OH vitamine D	nmol/L	ng/mL
Depletion [1]	**< 25**	**< 10**
Insufficiency [2]	**25 - 75**	**10 - 30**
Aimed levels [2]	**75 - 125**	**30 - 50**
Hypervitaminose [3]	**≥ 250**	**≥ 100**

1. Cormier. AFLAR. PNNS, http://www.sante.gouv.fr/htm/pointsur/nutrition/actions42_pa.pdf
2. McKenna. The American Journal of Medicine 1992 ; 93: 69-77.
3. Hollis BW. J Nutr 2005; 135: 317-22.

Armas L, Hollis B, Heaney R. Vitamin D2 is much less effective than vitamin D3 in humans. **J Clin Endocrinol Metab** 2004 ; 89 : 5387-91



Cholecalciferol(D3) ,longer T1/2 25.000 /week

Holick MF, Biancuzzo RM,Chen TC et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxy vitamin D **J Clin Endocrinol Metab** 2008 ; 93 : 677-681.

Effet du cholécalciférol (D3)100 000 mensuel en dialyse

G Jean et al,NDT(2009) 24: 3799–3805

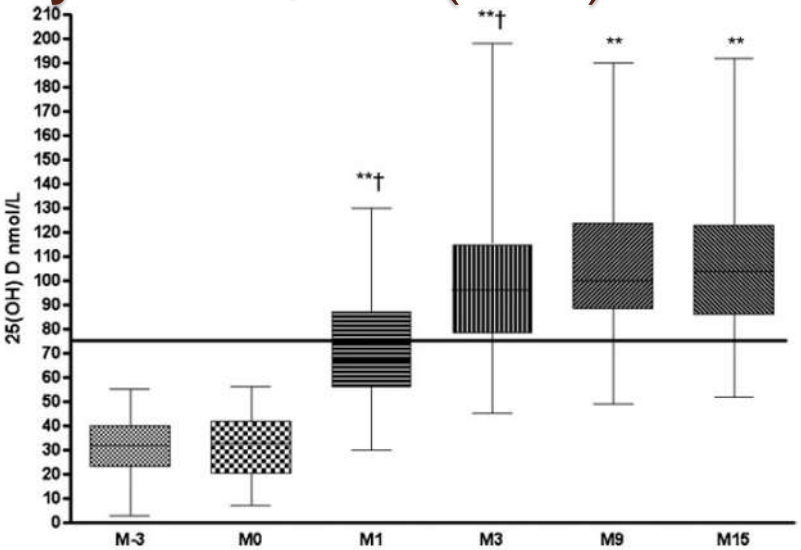


Fig. 1. Evolution of 25(OH)D serum levels (Box plot). $^{**}P < 0.001$ with baseline, $^{\dagger}P < 0.05$ with the previous value.

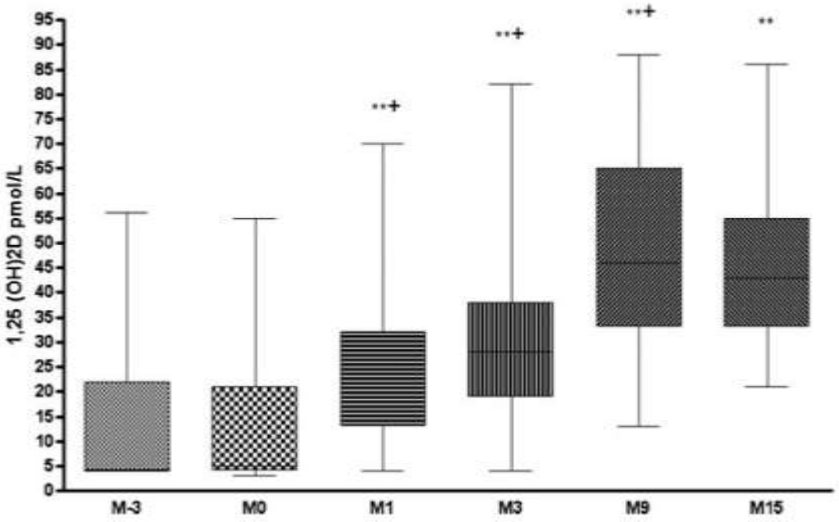


Fig. 2. Evolution of 1,25(OH)2D serum levels (Box plot). $^{**}P < 0.001$ with baseline, $^{\dagger}P < 0.05$ with the previous value.

Table 2. Changes in vitamin D and mineral metabolism parameters

Months	M-3	M0	M1	M3	M9	M15
25(OH)D (nmol/L) (range)	31 ± 11 (3–55)	32 ± 13 (7–56)	68.3 ± 19 (30–130)**,†	97.7 ± 28 (45–198)**,†	105.7 ± 28 (49–190)**	105.8 ± 27 (52–192)**
% 25(OH)D > 75 nmol/L	0	0	46**,†	82**,†	88**	91**
1,25(OH)$_2$D (pmol/L) (range)	14 ± 14 (4–56)	13.7 ± 14 (4–55)	23.8 ± 14 (4–70)**,†	30.7 ± 14 (4–82)**,†	49.2 ± 17 (13–88)**,†	45 ± 13 (21–86)**
PTH (pg/mL) (median, inter-quartile range)	294 (180–435)	295 (190–450)	249 (158–378)*,†	220 (113–300)*	200 (145–280)*	190 (110–273)*
BALP (μg/L) (range)	21 ± 10 (6–45)	20.5 ± 9 (7–41)	18.7 ± 9 (6–37)	16.5 ± 6 (6–35)*,†	17 ± 6 (8–35)*	17.1 ± 7 (6–35)*
β-cross-laps (μg/L) (range)	2.5 ± 1 (0.8–6)	2.5 ± 1 (0.9–5)	2.27 ± 1 (0.6–5)	2.1 ± 1 (0.64.8)*,†	2.05 ± 0.8 (0.7–4.2)*	2.07 ± 0.8 (0.5–4.1)*
Calcaemia (mmol/L) (range)	2.27 ± 0.14 (1.9–2.53)	2.24 ± 0.12 (2–2.5)	2.28 ± 0.1 (2 –2.53)	2.28 ± 0.1 (2–2.5)	2.25 ± 0.1 (2–2.53)	2.25 ± 0.1 (2–2.58)
Phosphataemia (mmol/L) (range)	1.34 ± 0.3 (0.8–2.2)	1.32 ± 0.3 (0.8–2)	1.36 ± 0.3 (0.7–2.3)	1.33 ± 0.3 (0.7–1.9)	1.36 ± 0.3 (0.8–1.9)	1.31 ± 0.3 (0.8–2.1)

$^{*}P < 0.05$, $^{**}P < 0.001$ with the previous value, $^{\dagger}P < 0.05$ with the baseline value.

Apports alimentaires

Très peu d'aliments contiennent de la vitamine D en quantité significative

	Ration quotidienne nécessaire pour couvrir les besoins [1,2]	Ration hebdomadaire nécessaire pour couvrir les besoins [1,2]
Huile de foie de morue	**1,5 cuillère** à café	**10,5 cuillères** à café
Girolles	**12 portions** de 60 g	**84 portions** de 60 g
Harengs au vinaigre	**2 portions** de 60 g	**14 portions** de 60 g
Sardines à l'huile	**20 sardines**	**140 sardines**
Œuf dur	**22 œufs** moyens	**154 œufs** moyens
Foie de veau	**50 tranches** de 100 g	**350 tranches** de 100 g
Beurre	**5 plaquettes** de 250 g	**35 plaquettes** de 250 g

1. AFSSA. Les apports nutritionnels conseillés pour la population française. 3e édition. Paris : Editions TEC & DOC ; 2001.
2. INRA. Répertoire général des aliments. Table de composition. 2e édition. Paris : Editions TEC & DOC ; 1995.

Cost-Effectiveness of Monitoring and Vitamin D Supplementation in CKD

Comparison with other CKD-MBD treatments

Type of Medication	Compound	Dose	Cost (Euros)/ Month
Phosphate Binders (calcium containing)	Calcium Carbonante Calcium Acetate	2 g/d 2 g/d	**17.10** **40.04**
Phosphate Binders (calcium free)	Sevelamer Lanthane Carbonate	4.8 g/d 3 g/d	**191.63** **237.56**
Calcimimetic	Cinacalcet	90 mg/d	**556.04**
Ergocalciferol	Sterogyl	100 000 IU/month	**0.37**
Cholecalciferol	Uvedose	100 000 IU/month	**2.02**

Vitamin D Supplementation in Chronic Kidney Disease: A Systematic Review and Meta-Analysis of Observational Studies and Randomized Controlled Trials

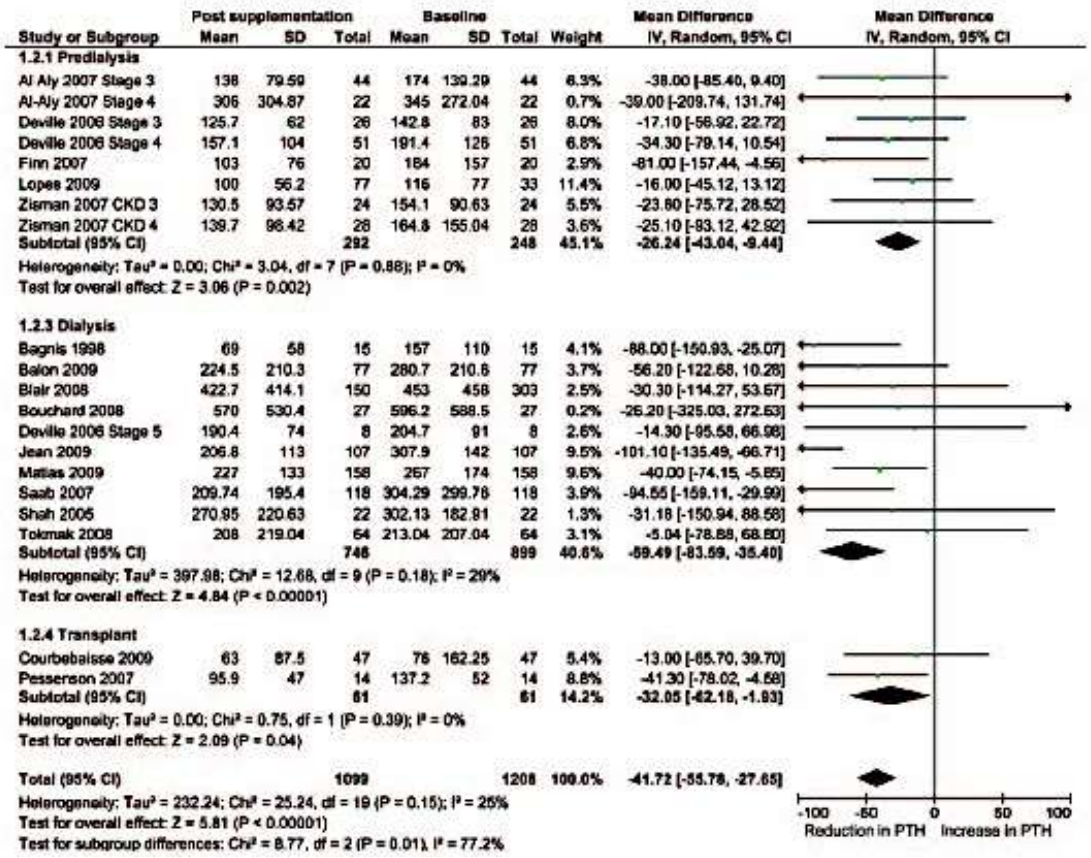


Figure 3. | Effect of vitamin D supplementation on PTH levels at the end of treatment period among observational studies in CKD.

Vitamin D supplementation appears to improve 25(OH)D and 1,25(OH)2D levels while reducing PTH levels without increasing the risk for hypercalcemia and hyperphosphatemia. However, whether such supplementation translates into better cardiovascular and skeletal outcomes needs to be evaluated in future studies.

VitD supplementation and PTH

Kandula P et al. CJASN 6:50-62, 2011

Table 2. Summary of prospective interventional studies assessing effect of vitamin D supplementation on cardiovascular disease endpoints in CKD

Study	Study Population	Intervention	Control	Duration	Cardiovascular endpoint(s) measured	Clinical relevance
Studies assessing left ventricular mass and function						
PRIMO Thadhani et al., 2012[47] and Tamez et al., 2012[48]	227 participants with stage 2-5 CKD and mild to moderate LVH	Paricalcitol	Yes	48 weeks	No change in LV mass Reduction in left atrial dilatation. Attenuated rise in BNP in treatment group. Fewer cardiovascular-related hospitalisations	Potential benefit in patients with impaired diastolic function. May reduce hospitalisations and mortality from CV causes.
Ivarsen et al., 2012[49]	14 participants with stage 4 CKD and LVH	Alfacalcidol	Yes	26 weeks	No change in LV mass LV systolic function improved in treatment group.	Potential benefit in patients with impaired systolic function.
OPERA Wang et al., 2014[50]	60 participants with stage 3-5 CKD and LVH	Paricalcitol	Yes	52 weeks	No change in LV mass, LV volume or LV systolic and diastolic function.	Long-term studies are required to verify effects on systolic and diastolic function.
Studies assessing endothelial function						
PENNY Zoccali et al., 2014[51]	88 participants with stage 3-4 CKD	Paricalcitol	Yes	12 weeks	FMD 61% higher in treatment group	Improved endothelial function with paricalcitol therapy; this may limit accelerated atherosclerosis in CKD
Chitalia et al., 2014[28]	26 participants with stage 3-4 CKD and serum 25(OH)D <75 nmol/L	Cholecalcife-rol	No	16 weeks	FMD 3% higher in treatment group Endothelial biomarkers concentration decreased	Overall improvement in endothelial function; this may limit accelerated atherosclerosis in CKD
Studies assessing vascular calcification						
Hewitt et al., 2013[40]	60 participants on haemodialysis and serum 25(OH)D ≤60 nmol/L	Cholecalcifer ol	Yes	6 months	No significant effect on pulse wave velocity	No significant reduction in vascular stiffness in patients with ESRD.
Levin et al., 2014[41]	128 participants with CKD	Calcitriol	Yes	6 months	Pulse wave velocity - *ongoing trial*	*Ongoing trial* – could vitamin D treatment reduce vascular stiffness, which is associated with poor CV disease outcomes?

Nephrology 2015 Vit D supplem and CV diseases

Impact of Vitamin D on Cardiovascular outcomes in Chronic Kidney Disease
Nephrology submitted 2015

Authors: Nadia Hussain, Huma Hosamuddin, Mohammed Oomerjee, Cristiana Vitale,Juan Carlos Kaski and Debasish Banerjee

Vitamin D is promising as an easily administered, cheap therapy to improve surrogate cardiovascular markers in patients with CKD, however further trials are necessary to prove its benefit in reducing CV mortality and morbidity.

Recently reported Effect of paricalcitol on left ventricular mass and function in CKD (theOPERAtrial) **did not find** a left ventricular mass difference for chronic administration of paricalcitol to patients with CKDstages 3 to5.
It improved secundary hyperparathroidism
JASN 25; 175; 2014

Paricalcitol Capsule Benefits in RenalFailure-Induced Cardiac Morbidity, a randomized controlled trial on a group of 227 patients with chronic kidney disease with mild-to-moderate left ventricular hypertrophy and preserved left-ventricular ejection fraction,**could not show** the influence of 48 weeks of paricalcitol therapy on the left ventricular mass in dexoron Doppler measures of diastolic dysfunction.
Am Heart J 164; 902; 2012
JAMA 307; 674; 2012

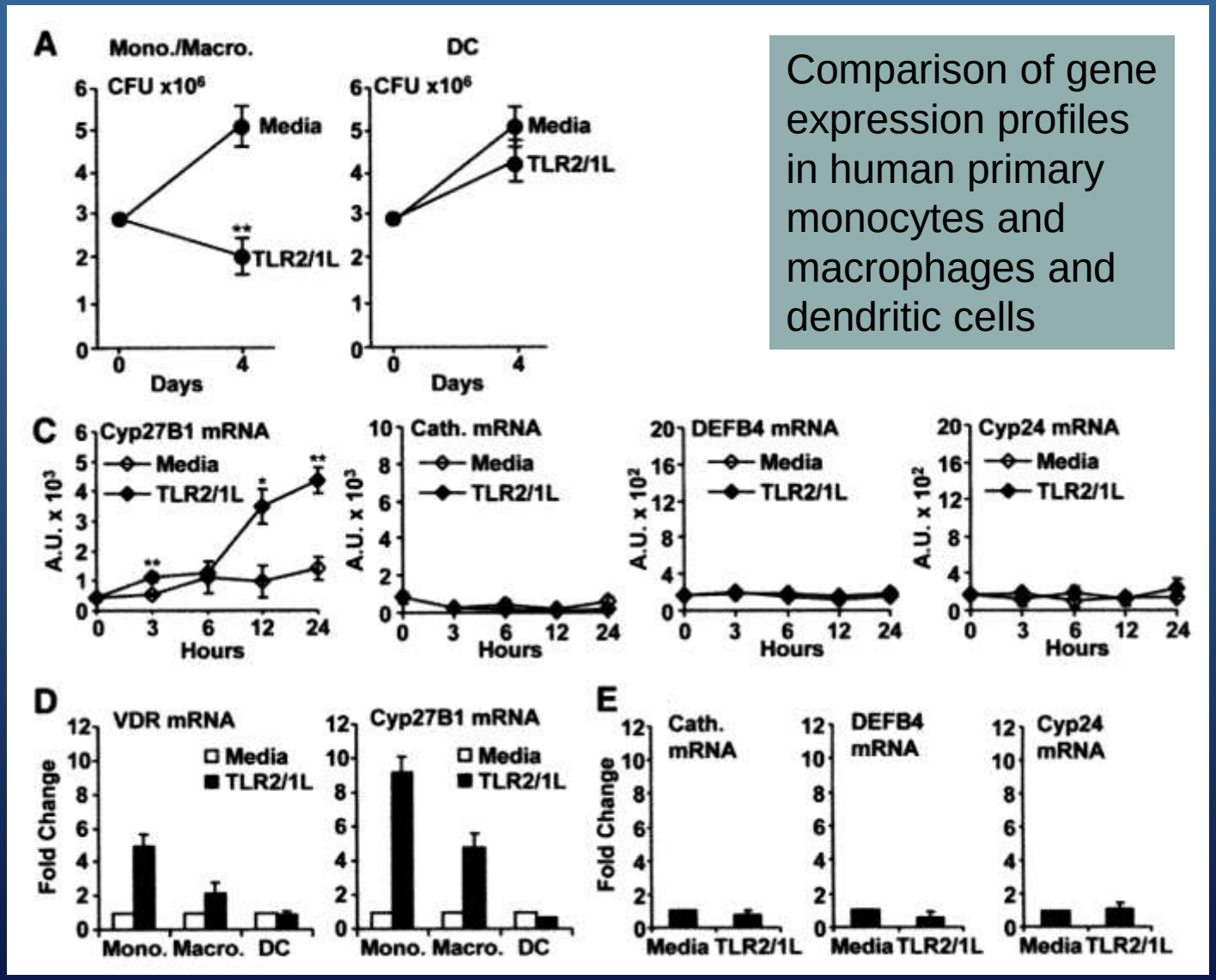
The fat lady has indeed finished singing, at least her first act.
Goldsmith D 2014 Sem. Nephrology

Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response

Infected cells
Myc Tuberc.

TLR2/1L :
Ligand: Mycob Tuberc derived peptide

Reduced viability

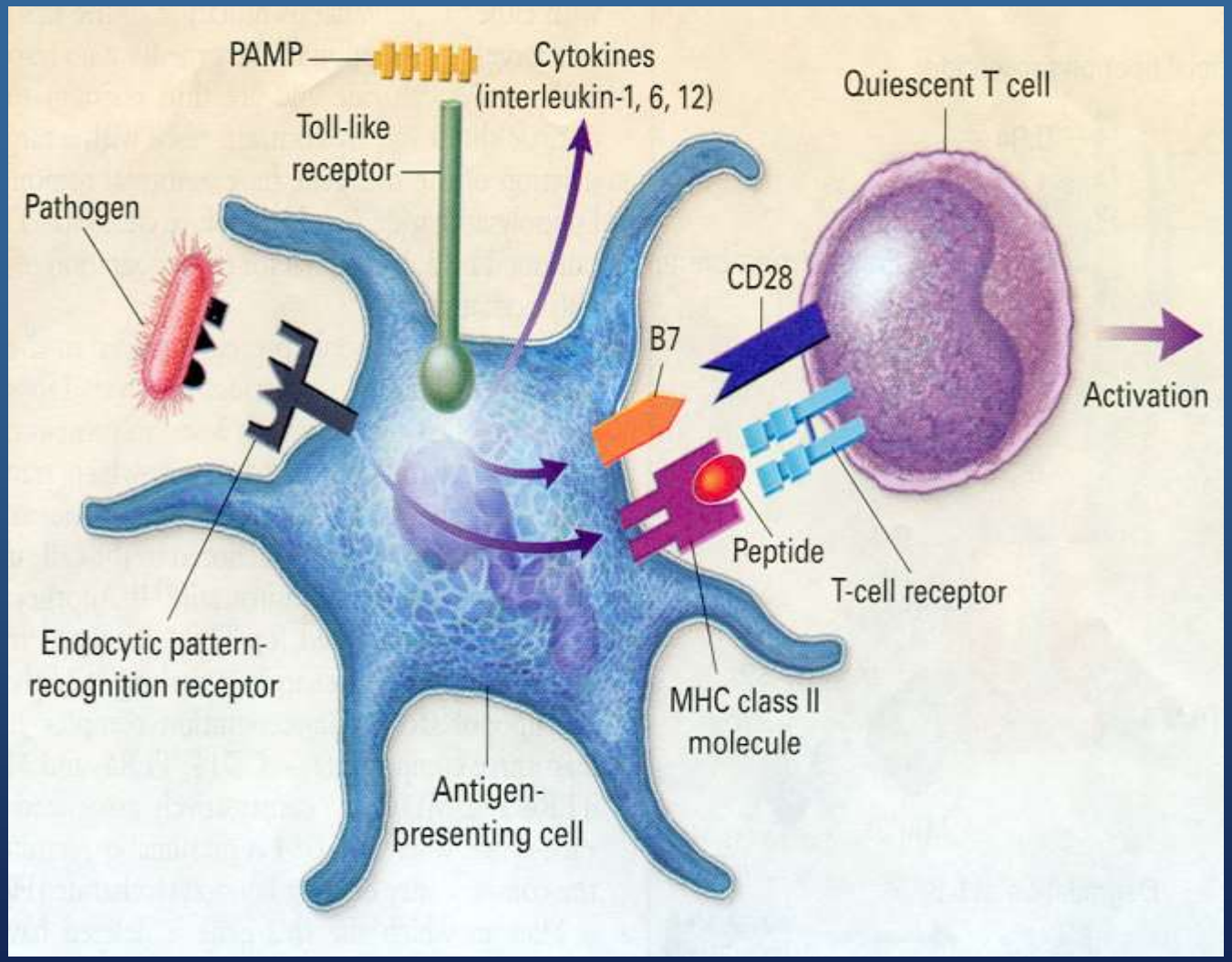


Comparison of gene expression profiles in human primary monocytes and macrophages and dendritic cells

Liu PT et al: Science 311: 1770-3, 2006

DDW3576

Innate immunity



In the case of the signaling class of pattern-recognition receptors,
the recognition of pathogen-associated molecular patterns by toll-like receptors leads
to the activation of signaling pathways that
induce the expression of cytokines, chemokines, and costimulatory molecules.

Medzhitov R & Janeway C:
New Engl J Med 343: 338-343, 2000

Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response

Infected cells
Myc Tuberc.

TLR2/1L :
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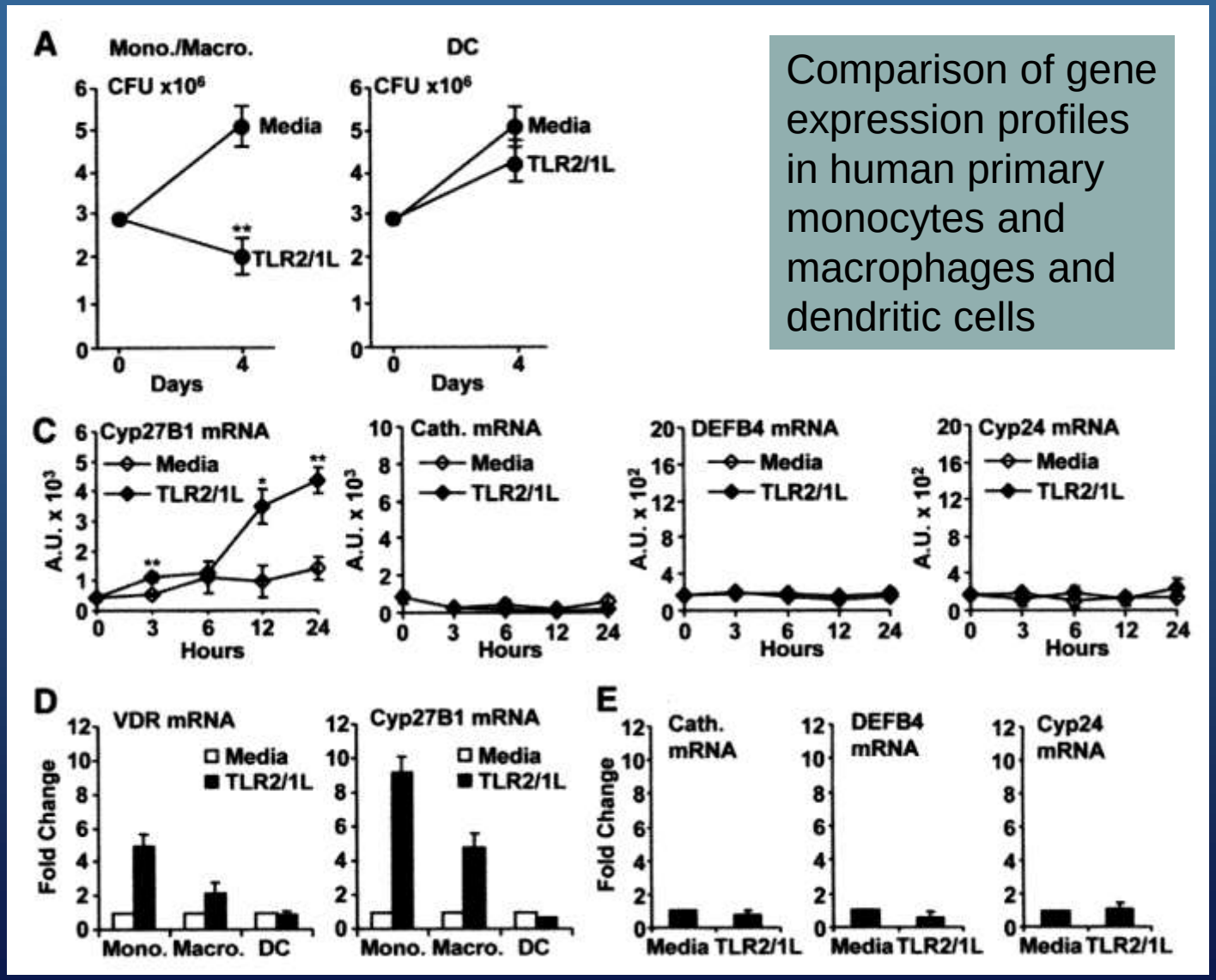

Comparison of gene expression profiles in human primary monocytes and macrophages and dendritic cells

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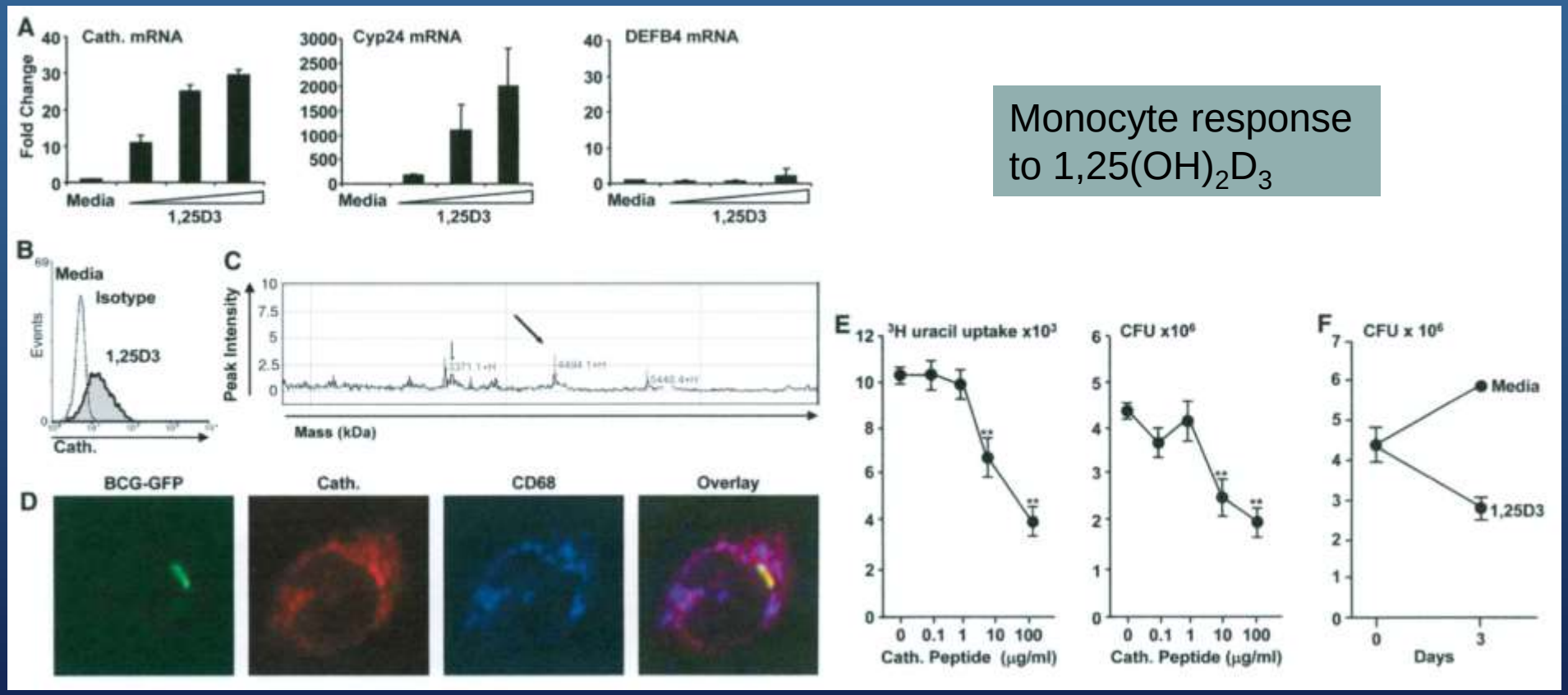
Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response



Monocyte response to $1,25(OH)_2D_3$

Cath=Cathelicidin

Liu PT et al: Science 311: 1770-3, 2006

DDW3576

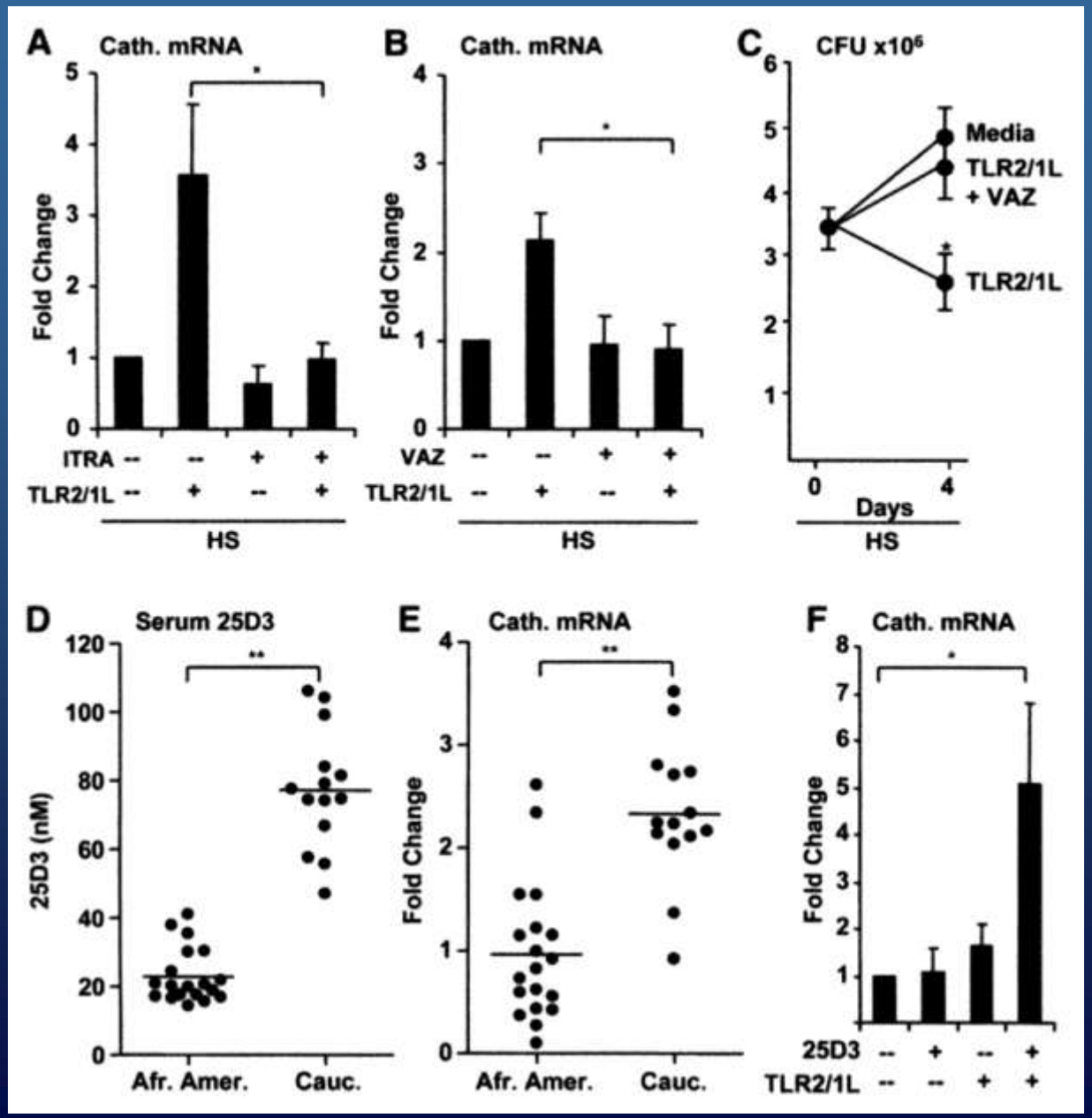
Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response

Role of the vitamin D pathway in induction of cathelicidin mRNA and antimicrobial activity

TLR2/1=toll like receptors

TLR2/1L=synt lipopeptide

VAZ=VDR antagonist



Liu PT et al: Science 311: 1770-3, 2006

DDW3576

Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response

- We also observed that sera from African-American individuals,
- known to have increased susceptibility to tuberculosis, had low
- 25-hydroxyvitamin D and were inefficient in supporting
- cathelicidin messenger RNA induction.

- These data support a link between TLRs and vitamin D–mediated innate immunity and suggest that differences in ability of human populations to produce vitamin D may contribute to susceptibility to microbial infection

Liu PT et al: Science 311: 1770-3, 2006

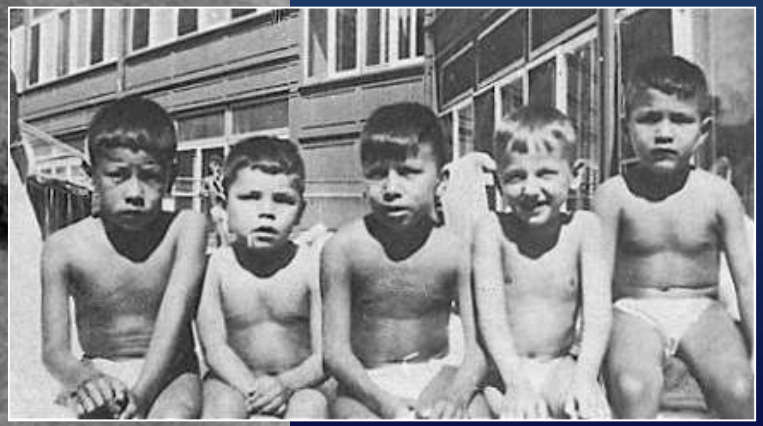
Sunlight treatment for tuberculosis

Brehmer & Trudeau

Niels Ryberg Finsen

Denmark

Nobel Prize 1903



DDW3655

: Pleiotropic effects of vitamin D

Vitamin D and analogs in mineral metabolism:

- Suppression of cell growth
- Regulation of apoptosis
- Modulation of immune response
- Control of insulin secretion
- Control of Calcium and P metabolism
- Tuberculosis

Conclusion

- **Vitamin D is a hormonal system implicated in many gene control systems (deficiency, insufficiency, intoxication)**
- **Numerous targets** (os, système cardiovasculaire, immunité, diabète, rein, muscle, cerveau…) **favorable effect on survival**
- In CKD : **variable but almost constant deficiency 25(OH)D et 1,25(OH)2D**
- 1 alfa Hydroxylation ubiquitous + direct effect of 25(OH)D **= justification of supplémentation in native vitamine D in 1^{the} intention:**
- simple, cheap, well tolerated
- **CKD : decrease of PTH and other bone markers even with natural VitD.**
- **CVD and CKD effect of VitD TO BE PROVEN**

Ophrys Insectifera, Ophrys mouche , rare

La vitamine D native optimale

« Absorption quotidienne ou production suffisante pour que sa disponibilité ne soit un frein à aucun métabolisme dépendant de la vitamine D mais qu'aucune toxicité n'apparaisse. »

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Chandra 2008	270	190.13	10	346	227.88	10	1.9%	-76.00 [-259.94, 107.94]
Dogan 2008	279	179	20	288	194	20	4.9%	-9.00 [-124.69, 106.69]
Siebert 2007	177.1	117	19	182.2	135.5	19	10.0%	-5.10 [-85.60, 75.40]
Wissing 2005	54	32	38	89	85	41	83.2%	-35.00 [-62.94, -7.06]
Total (95% CI)			87			90	100.0%	-31.53 [-57.01, -6.05]

Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 3 (P = 0.84); I² = 0%

Test for overall effect: Z = 2.42 (P = 0.02)

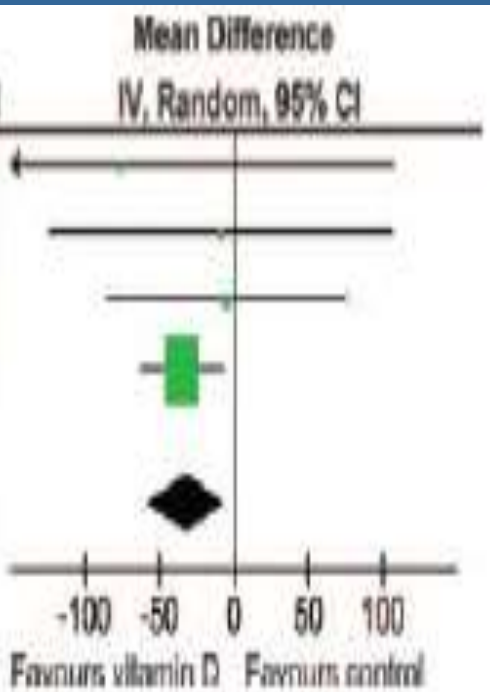


Figure 4. | Effect of vitamin D supplementation on PTH levels at the end of treatment period among RCTs in CKD.

Vitamin D Supplementation in Chronic KidneyDisease: A Systematic Review and Meta-Analysis of Observational Studies and Randomized Controlled Trials
25(OH);1,25(OH) D , PTH, hypercalcemia, hyperphosphatemia

Kandula et al CJASN 2011

Available evidence from low-to-moderate quality observational studies and fewer RCTs suggests that vitamin D supplementation improves biochemical endpoints. However, whether such improvements translate into clinically significant outcomes is yet to be determined.

Table 1. Selected Oral Cholecalciferol Pulse Dosing Studies in Patients With Kidney Failure Requiring Hemodialysis

Study	No. Randomly Assigned to Vitamin D_3	Equivalent Vitamin D_3 Dose (IU/wk)	Duration (wk)	Total Dose (IU)	Baseline Serum 25(OH)D (ng/mL)	Final Serum 25(OH)D (ng/mL)	Vitamin D Sufficient (%)
Armas et al[8] (2012)	20	10,333	15	154,995	13.3	36.9	NR
Delanaye et al[9] (2013)	16	12,500	52	650,000	12	33	75
Tokmak et al[10] (2008)	64	20,000	36	720,000	6.6	31.8	57
Jean et al[11] (2009)	107	25,000	64	1,600,000	12.8	42.3	91
Massart et al[7] (2014)	26	25,000	13	325,000	17.1	35.2	61.5
Marckmann et al[12] (2012)	13	40,000	8	320,000	8.3	54	100
Wasse et al[13] (2012)	25	200,000	3	600,000	14.3	52.4	91

Note: Mean values reported except for Armas et al[8] and Delanaye et al,[9] which reported median values.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; NR, not reported.

AJKD 2014; 64; 667 **Natural Vitamin D2 an 3**

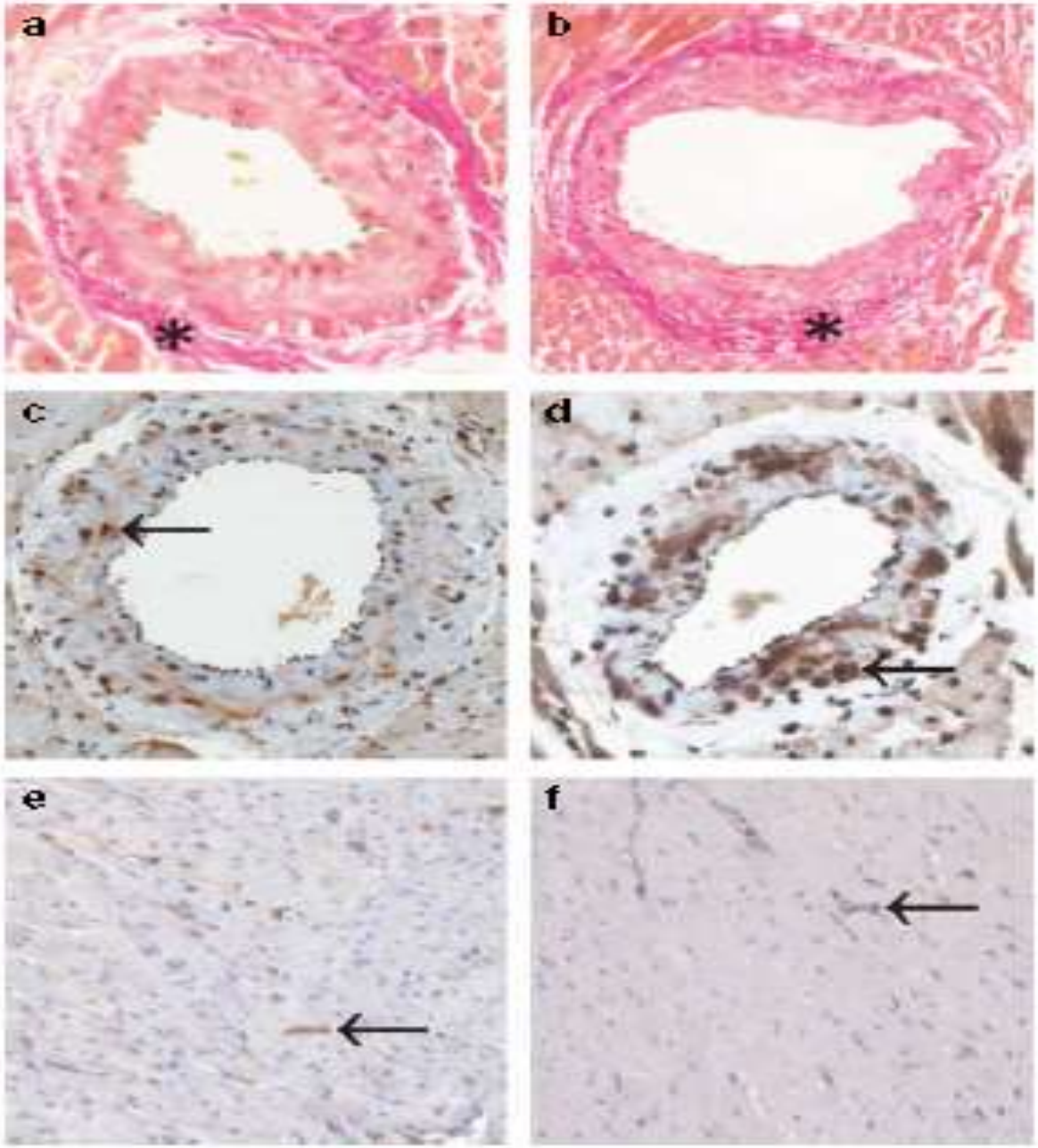


Figure 4 | Cardiac histology. Representative original photomicrographs showing cardiac perivascular fibrosis

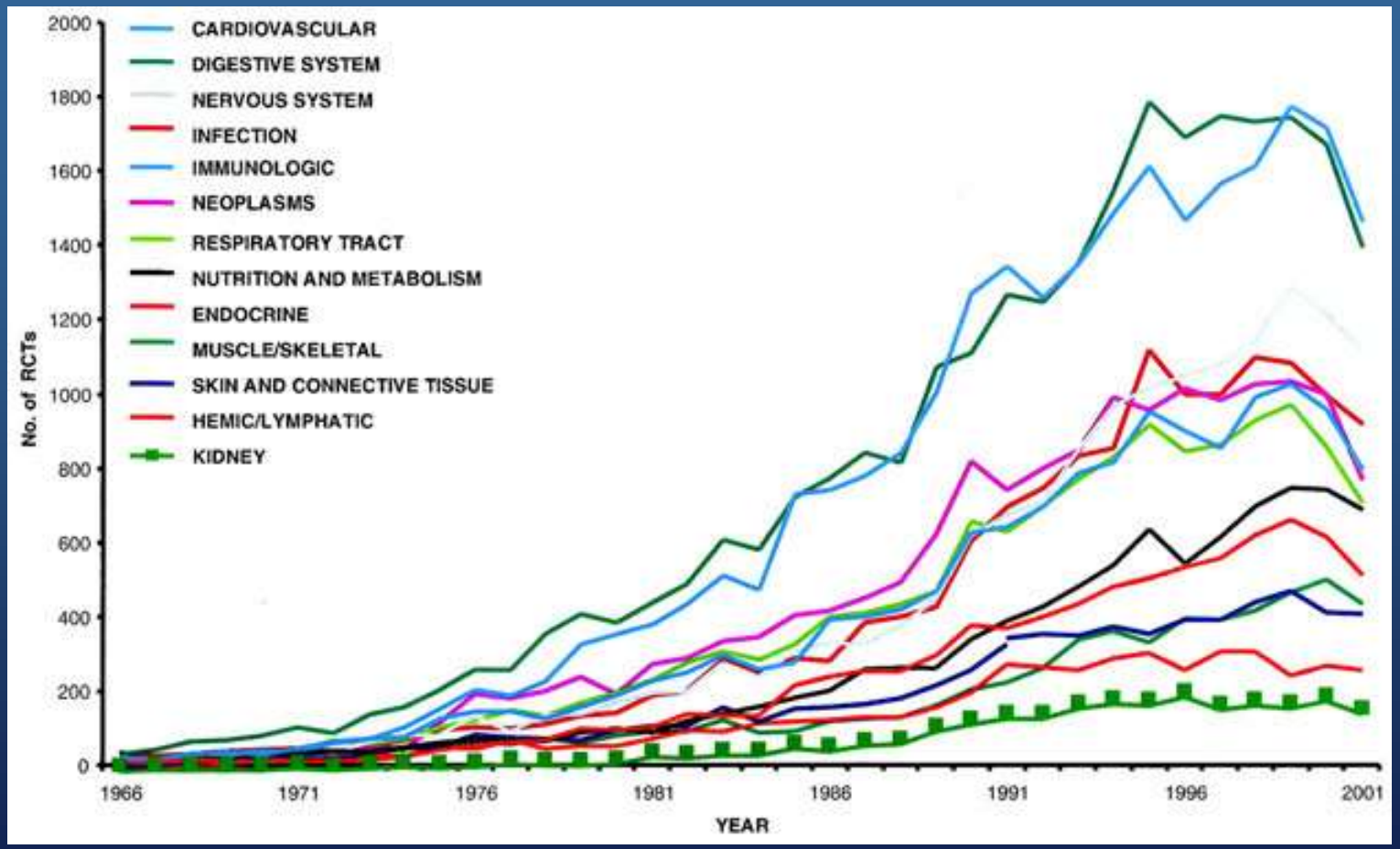
Paricalcitol aggravates perivascular fibrosis in rats with renal insufficiency and low calcitriol

JM Repo1, IS Rantala2, TT Honkanen2, JT Mustonen3,4, P Ko¨o¨ bi5, AM Tahvanainen3,4, OJ Niemela¨6,
I Tikkanen7,8, JM Rysa¨9, HJ Ruskoaho9 and IH Po¨ rsti3,4

Kidn Intern. 72; 979 ;2007

Cardiac perivascular fibrosis and connective
tissue growth factor were significantly increased in the remnant kidney groups, and further increased in paricalcitoltreated
rats.

The number, quality, and coverage of randomized controlled trials in nephrology

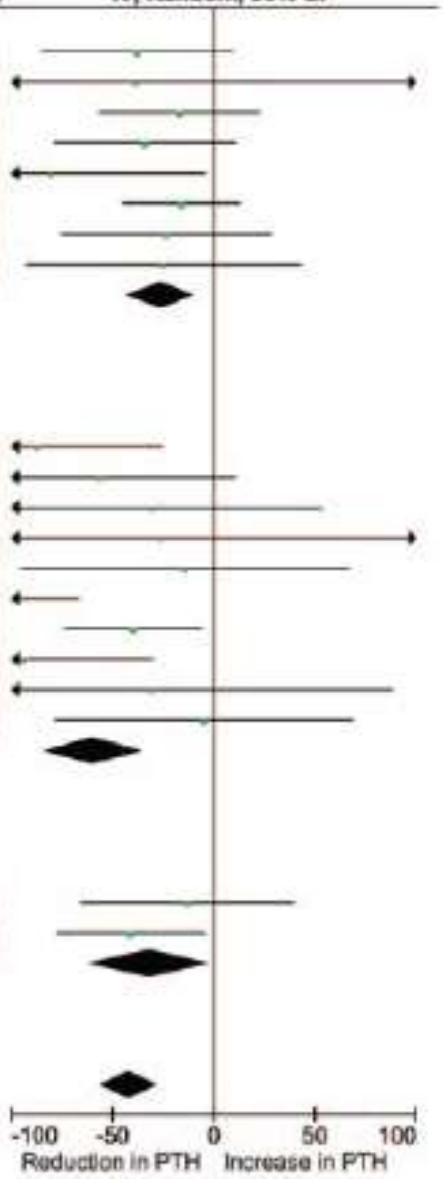


Number of randomized controlled trials (RCT) published in nephrology and 12 other specialties of internal medicine from 1966 to 2002

Strippoli GF: JASN 15: 411-419, 2004

3565

Study or Subgroup	Post supplementation Mean	SD	Total	Baseline Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Predialysis								
Al Aly 2007 Stage 3	136	79.59	44	174	139.29	44	6.3%	-38.00 [-85.40, 9.40]
Al-Aly 2007 Stage 4	306	304.87	22	345	272.04	22	0.7%	-39.00 [-209.74, 131.74]
Deville 2006 Stage 3	125.7	62	26	142.8	83	26	8.0%	-17.10 [-56.92, 22.72]
Deville 2006 Stage 4	157.1	104	51	191.4	126	51	6.8%	-34.30 [-79.14, 10.54]
Finn 2007	103	76	20	184	157	20	2.9%	-81.00 [-157.44, -4.56]
Lopes 2009	100	56.2	77	116	77	33	11.4%	-16.00 [-45.12, 13.12]
Zisman 2007 CKD 3	130.5	93.57	24	154.1	90.63	24	5.5%	-23.60 [-75.72, 28.52]
Zisman 2007 CKD 4	139.7	98.42	28	164.8	155.04	28	3.6%	-25.10 [-93.12, 42.92]
Subtotal (95% CI)			292			248	45.1%	**-26.24 [-43.04, -9.44]**
Heterogeneity: Tau² = 0.00; Chi² = 3.04, df = 7 (P = 0.88); I² = 0%								
Test for overall effect: Z = 3.06 (P = 0.002)								
1.2.3 Dialysis								
Bagnis 1998	69	58	15	157	110	15	4.1%	-88.00 [-150.93, -25.07]
Balon 2009	224.5	210.3	77	280.7	210.6	77	3.7%	-56.20 [-122.68, 10.28]
Blair 2008	422.7	414.1	150	453	458	303	2.5%	-30.30 [-114.27, 53.67]
Bouchard 2008	570	530.4	27	596.2	588.5	27	0.2%	-26.20 [-325.03, 272.63]
Deville 2006 Stage 5	190.4	74	8	204.7	91	8	2.6%	-14.30 [-95.58, 66.96]
Jean 2009	206.8	113	107	307.9	142	107	9.5%	-101.10 [-135.49, -66.71]
Matias 2009	227	133	158	267	174	158	9.6%	-40.00 [-74.15, -5.85]
Saab 2007	209.74	195.4	118	304.29	299.76	118	3.9%	-94.55 [-159.11, -29.99]
Shah 2005	270.95	220.63	22	302.13	182.91	22	1.3%	-31.18 [-150.94, 88.58]
Tokmak 2008	208	219.04	64	213.04	207.04	64	3.1%	-5.04 [-78.88, 68.80]
Subtotal (95% CI)			746			899	40.6%	**-59.49 [-83.59, -35.40]**
Heterogeneity: Tau² = 397.96; Chi² = 12.68, df = 9 (P = 0.18); I² = 29%								
Test for overall effect: Z = 4.84 (P < 0.00001)								
1.2.4 Transplant								
Courbebaisse 2009	63	87.5	47	76	162.25	47	5.4%	-13.00 [-65.70, 39.70]
Pessenson 2007	95.9	47	14	137.2	52	14	8.8%	-41.30 [-78.02, -4.58]
Subtotal (95% CI)			61			61	14.2%	**-32.65 [-62.18, -1.93]**
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 1 (P = 0.39); I² = 0%								
Test for overall effect: Z = 2.09 (P = 0.04)								
Total (95% CI)			1099			1208	100.0%	**-41.72 [-55.78, -27.65]**
Heterogeneity: Tau² = 232.24; Chi² = 25.24, df = 19 (P = 0.15); I² = 25%								
Test for overall effect: Z = 5.81 (P < 0.00001)								
Test for subgroup differences: Chi² = 8.77, df = 2 (P = 0.01), I² = 77.2%								



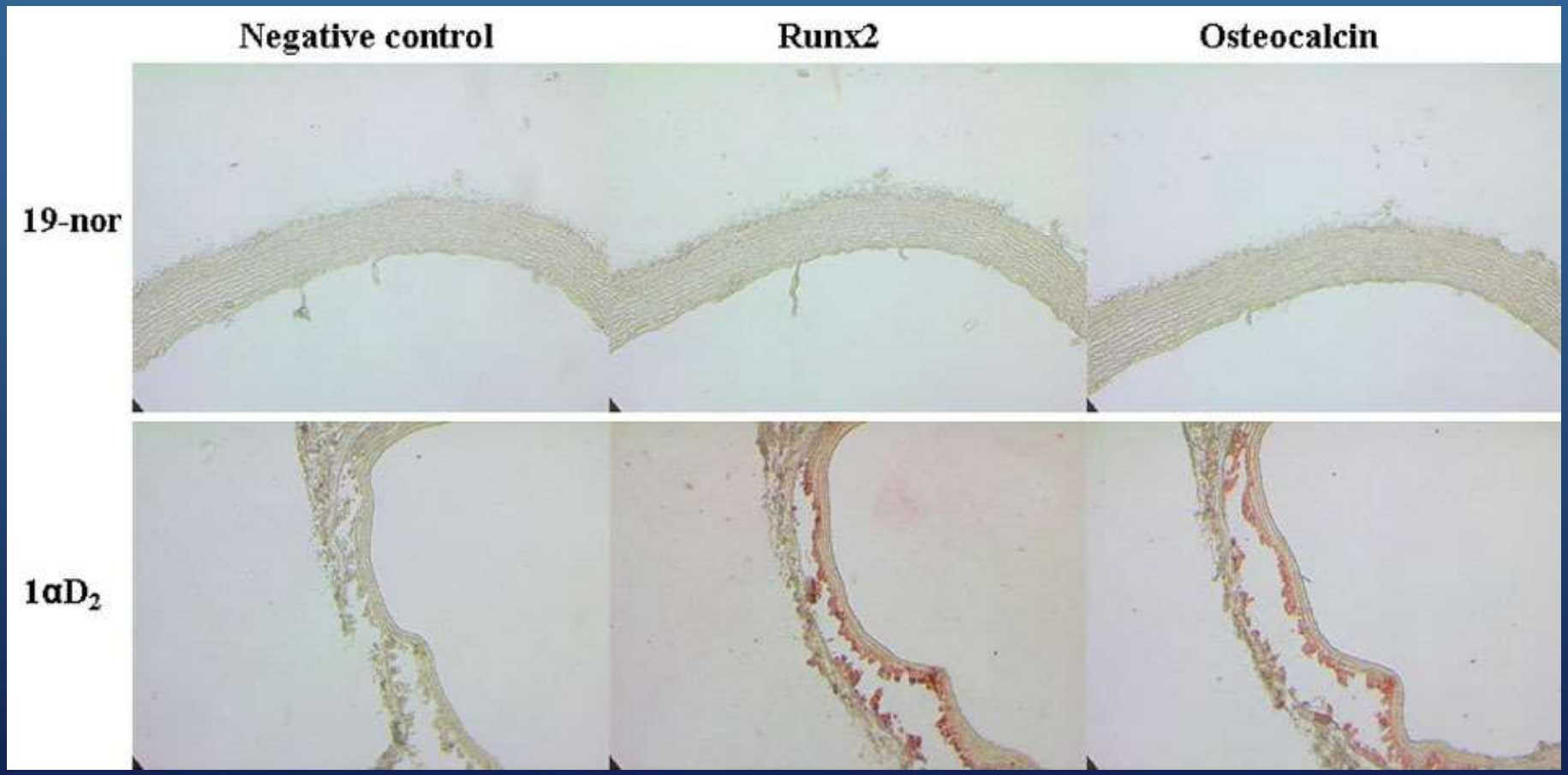
CJASN 2011

Figure 3. | Effect of vitamin D supplementation on PTH levels at the end of treatment period among observational studies in CKD.

CONCLUSIONS

- Low bone turn over seems to favor development of vascular calcifications.
- PTH seems not to play a direct role in the development of vascular calcifications.
- Calcimimetics and vascular calcifications ?
- Bisphosphonates are powerful protectors against the development of vascular calcifications.
- Paricalcitol looks a promising Vit D : lowering PTH synthesis in the ABSENCE of hypercalcemia and increase(mRNA,protein) of cbfa1 abd osteocalcin.

Differential effects of vitamin D receptor activators on vascular calcification in uremic rats



Immunohistochemistry in aorta

Mizobuchi M et al: Kidney Int: in press 2007

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ERIK
DIRK
PATRICK

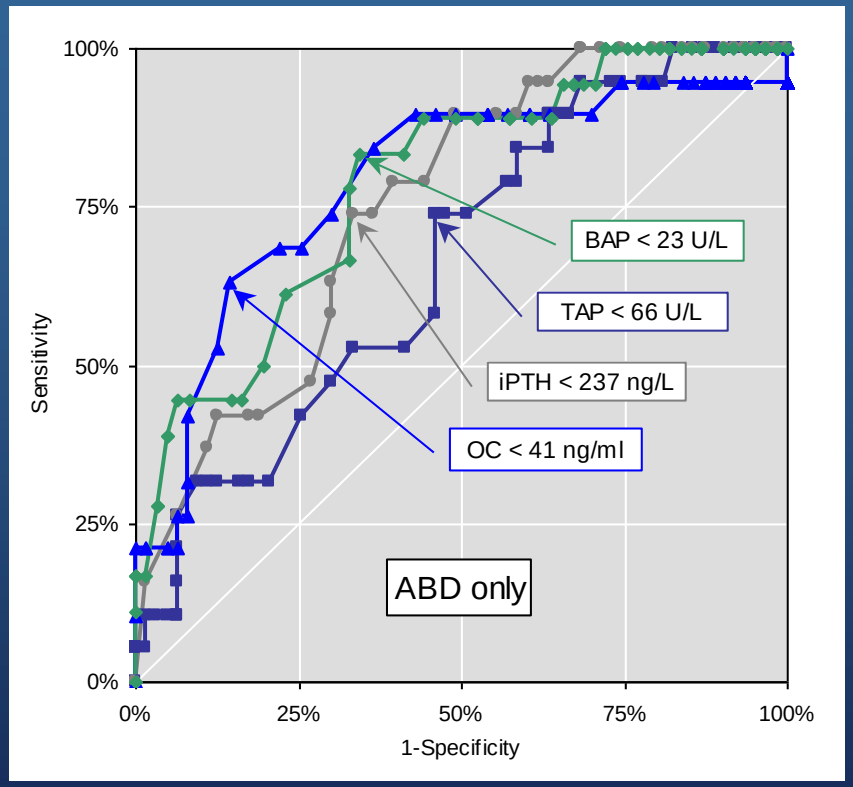
Posologies

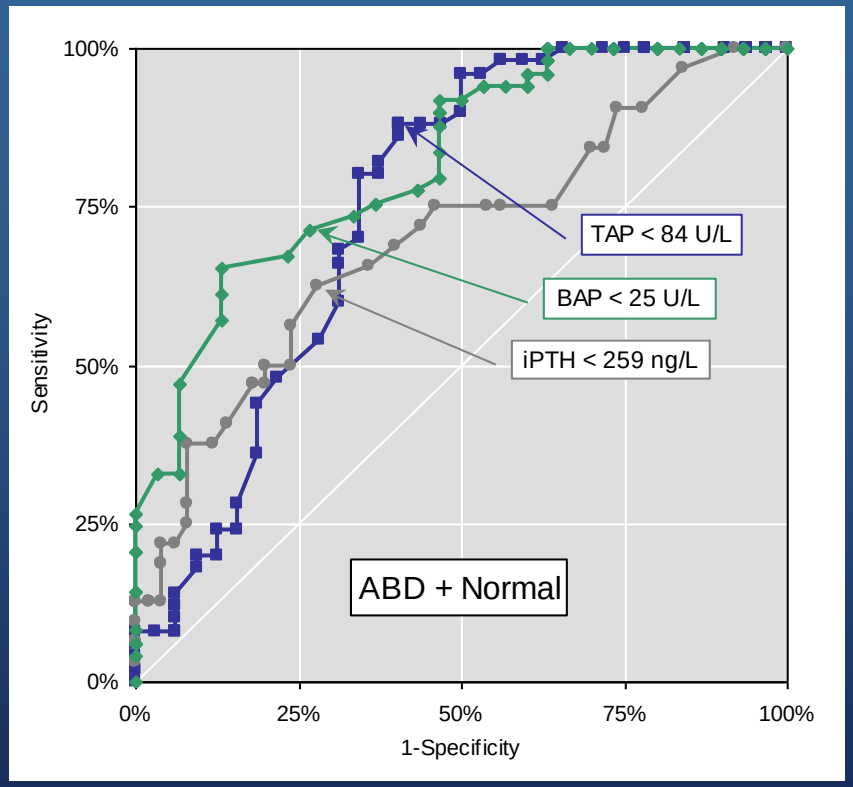
(Holick M. N Engl J Med 2007;357:266-81)

Table 3. (Continued.)

Cause of Deficiency†	Preventive and Maintenance Measures to Avoid Deficiency	Treatment of Deficiency
Adults		
Primary or tertiary hyperparathyroidism	800–1000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 2 wk (serum calcium levels will not increase),[115] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk‡	50,000 IU of vitamin D_2 once a wk for 8 wk; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml
Nephrotic syndrome[2,3,6,7,91-94]	1000–2000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 once or twice/wk,[2,94] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk[2]‡	50,000 IU of vitamin D_2 twice/wk for 8–12 wk[2,94]; repeat for another 8–12 wk if 25-hydroxyvitamin D <30 ng/ml‡
Chronic kidney disease§		
Stages 2 and 3	Control serum phosphate,[6] 1000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 2 wk,[91,94] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk; may also need to treat with an active vitamin D analog when vitamin D sufficiency is obtained‡	50,000 IU of vitamin D_2 once/wk for 8 wk[91,94]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Stages 4 and 5	1000 IU of vitamin D_3/day,[51] 50,000 IU of vitamin D_2 every 2 wk, need to treat with 1,25-dihydroxyvitamin D_3 or active analogue‡	0.25–1.0 μg of 1,25-dihydroxyvitamin D_3 (calcitriol)[2,6,91,93,94] by mouth twice a day or one of the following: 1–2 μg of paricalcitriol IV every 3 days,[6,91,93,94] 0.04–0.1 μg/kg IV every other day initially and can increase to 0.24 μg/kg, 2–4 μg by mouth three times/wk,[6,91,93,94] or doxecalciferol[6,91,93,94] 10–20 μg by mouth three times/wk or 2–6 μg IV three times/wk

Biochemical markers for diagnosing ROD in predialysis ESRF patients: *ROC curves*





ROC curves for BAP, TAP, iPTH and OC levels in the diagnosis of ABD (left), or ABD and normal bone considered one group (right) vs. other types of ROD.

Bervoets AR et al: Am J Kidney Dis 41: 997-1007, 2003

What is True?

1 Metformin is metabolized in the liver

2 Metforlin is not accumulated in patients with rnal failure

3 Metformin may accelerate tghe progression of kidney damage in patients with CKD3-5

4 Metformin may induce a lactic acidosis under paricular conditions

5 Metformin is an expensive drug

Correct answer nr 4

What is TRUE?

1 Vit D is inducing hypocalcemia in CKD patients

2 Vit D stimulates PTH at gene transcriptional level

3 Natural vit D inhibits PTH in CKD hyperparathyroidism

4 Vit D prolongs the life of CKD patients in Randomized Clinical Trials

5 Paricalcitol is a synthetic Vit D with less side effects on the calcium – phosphate metabolism in CKD patients, compared to other synthetic preparations.

Correct answer is nr 3

What is True?

1 CKD 3 according to the KDIGO guidelines is eGFR < 60ml/min /1.73m2 and proteinuria.

2 Proteinuria is a stable phenomenon particularly in his mild form

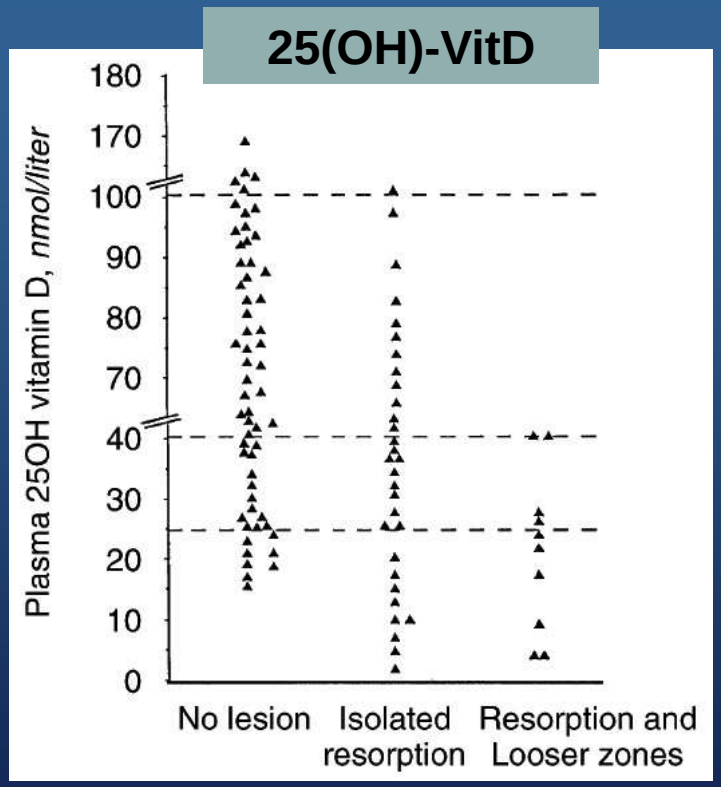
3 CKD5 patients are mainly women.

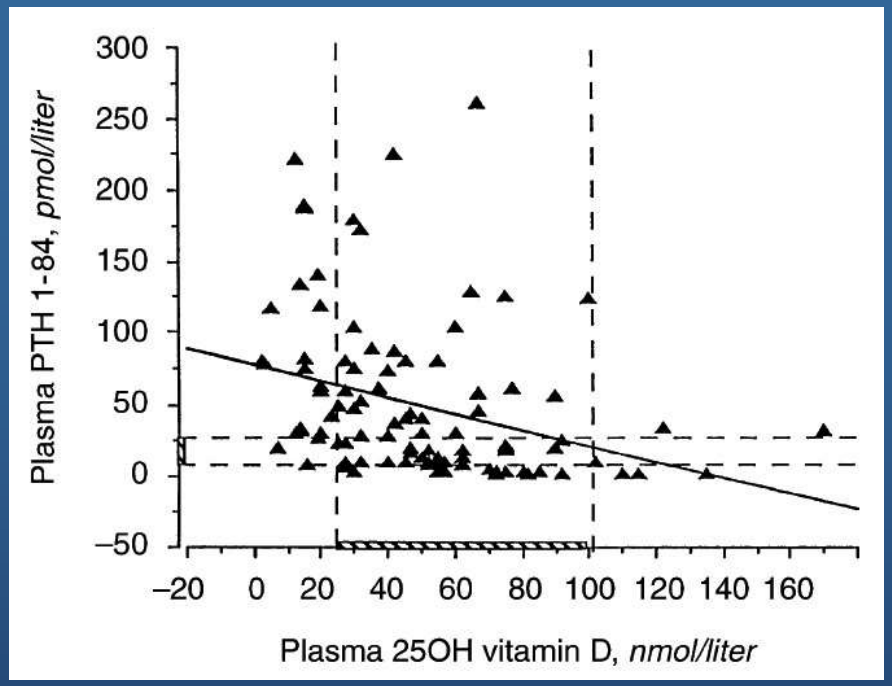
4 Confirming proteinuria and “chronicity” of decreasd eGFR is essential before considering an individual as having CKD.

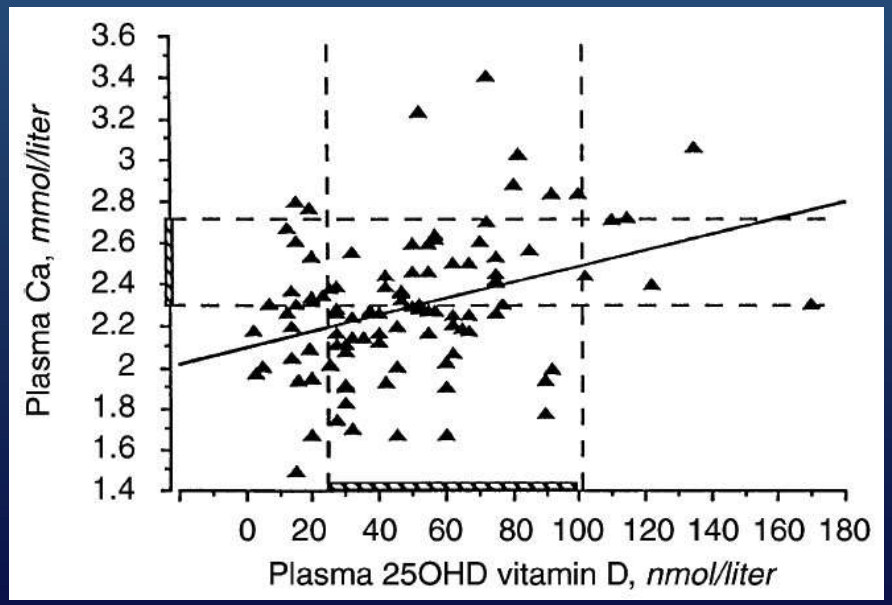
5 Majority of individuals with CKD4-5 have mild or overt proteinuria

Correct answer nr 5

Is low plasma 25-(OH)vitamin D a major risk factor for hyperparathyroidism and Looser's zones independent of calcitriol?







Ghazali A et al, Kidney Int 55: 2169-2177, 1999

DDW3569