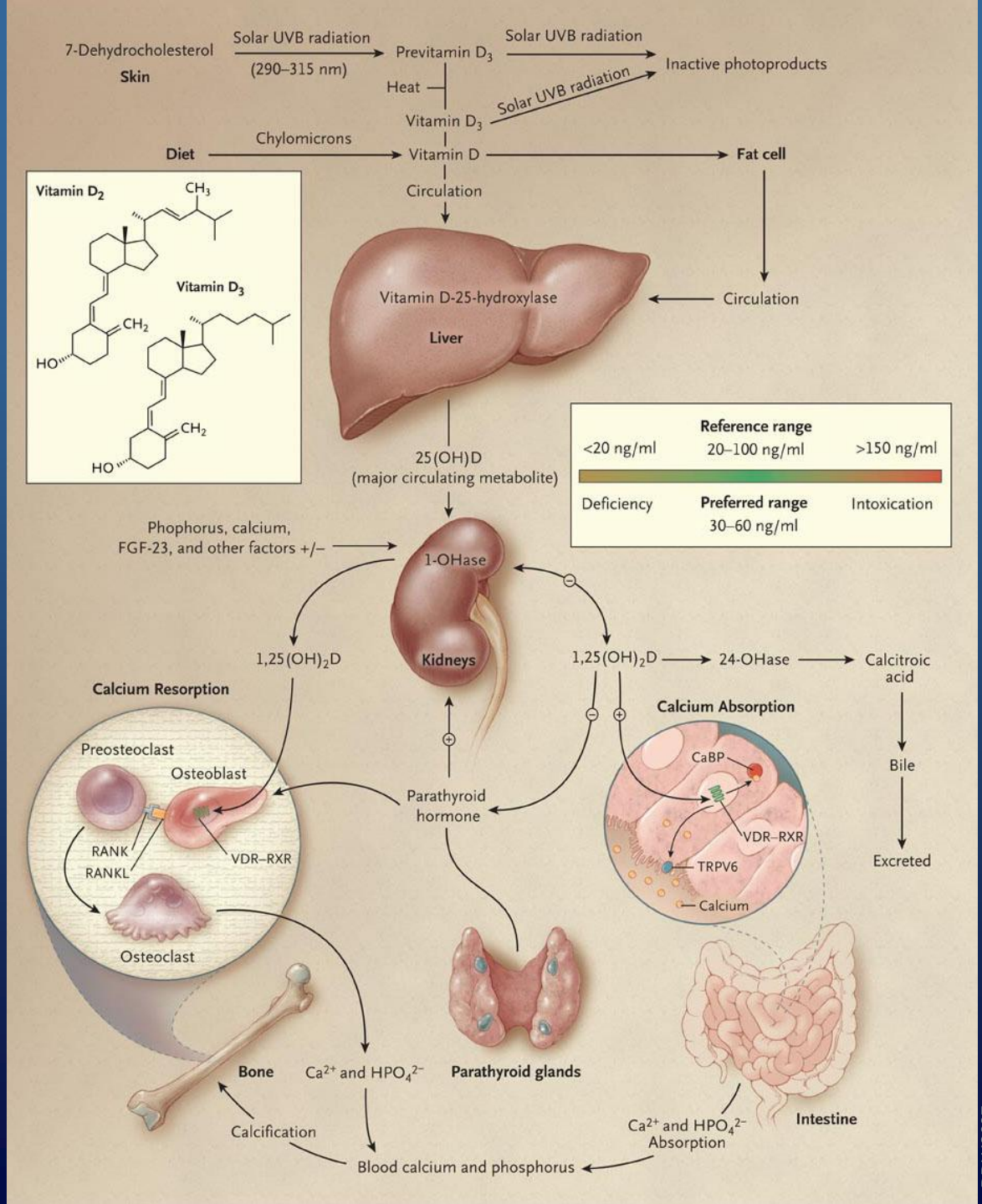
VITAMIN D

Budapest august 2012

Marc De Broe MD PhD

Vitamin D deficiency

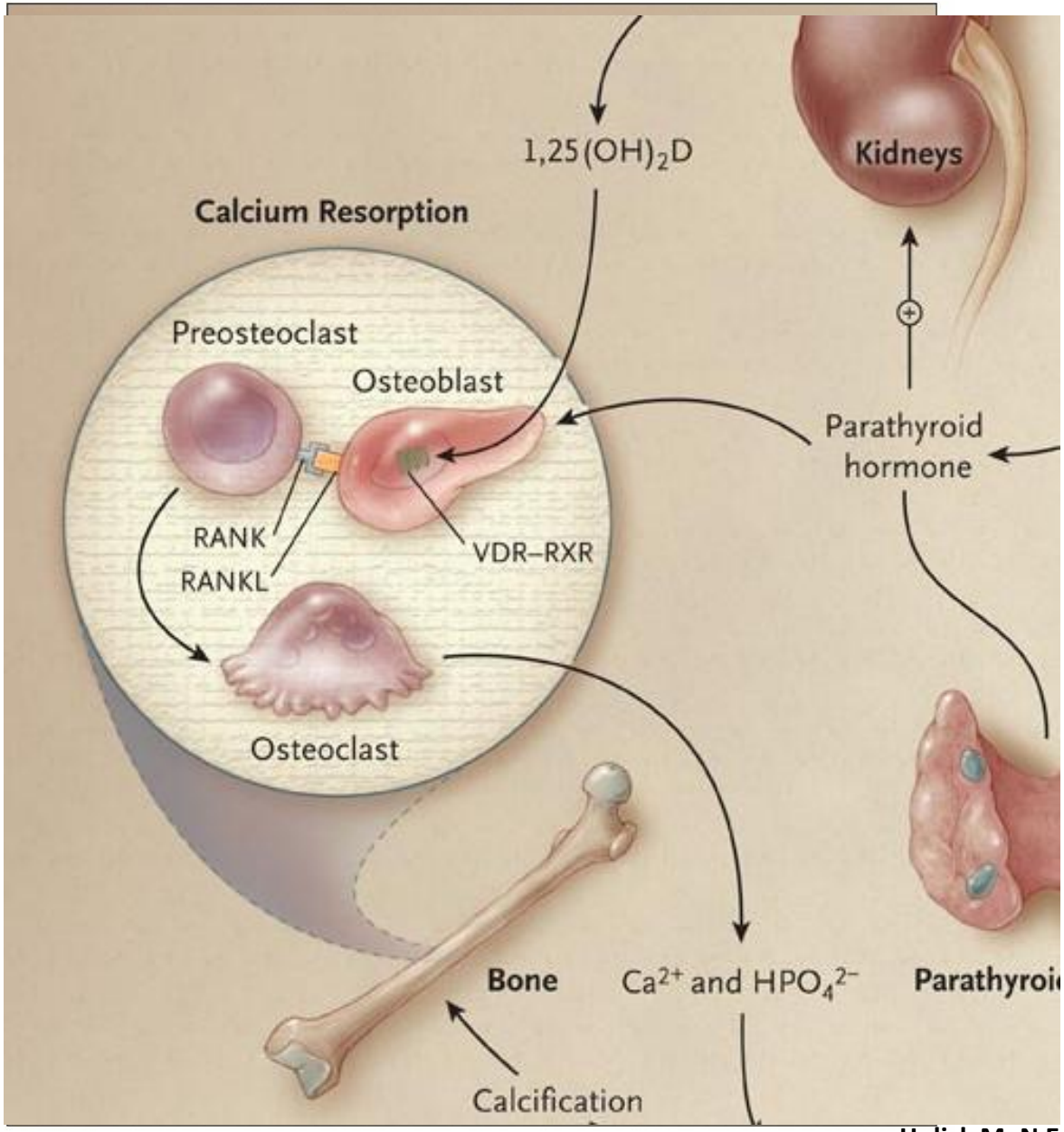


Synthesis and metabolism of vitamin D in the regulation of calcium, phosphorus, and bone metabolism

Holick MF: NEJM 357: 266-281, 2007

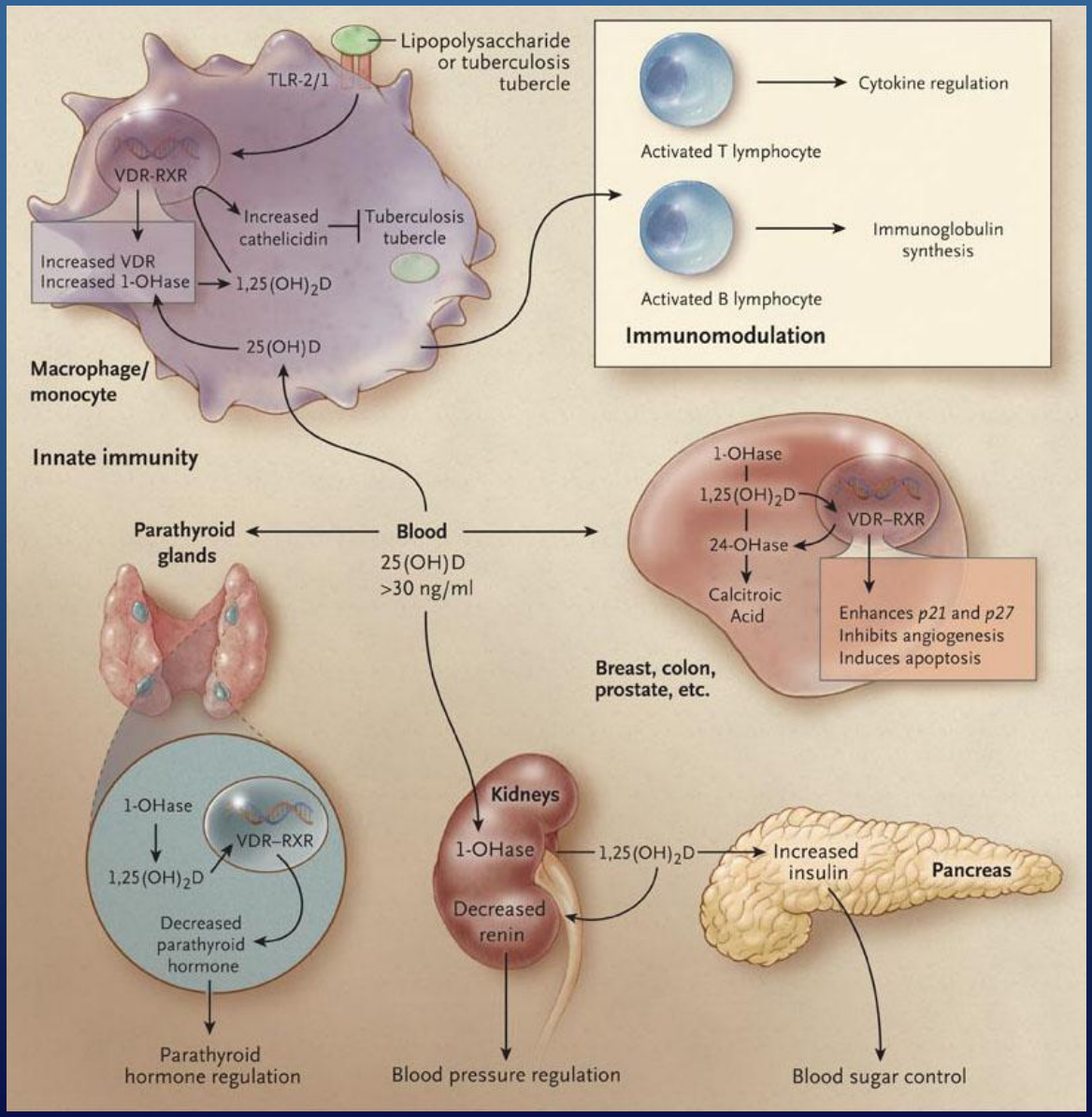
DDW3607

Vitamine D et Métabolisme Minéral et Osseux



Holick M. N Engl J Med 2007;357:266-281

Vitamin D deficiency

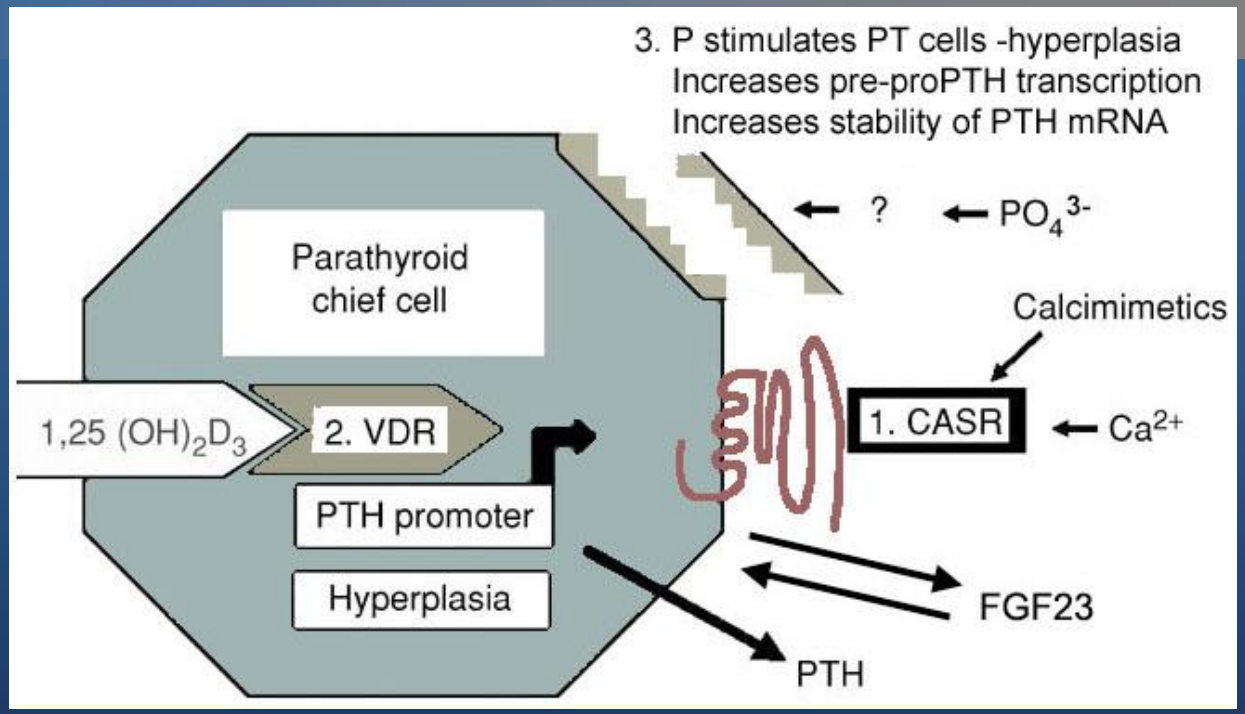


Metabolism of 25-Hydroxy-vitamin D to 1,25-Dihydroxy-vitamin D for Nonskeletal Functions

Holick MF: NEJM 357: 266-281, 2007

DDW3607

PTH secretion, PTH gene expression, parathyroid gland hyperplasia

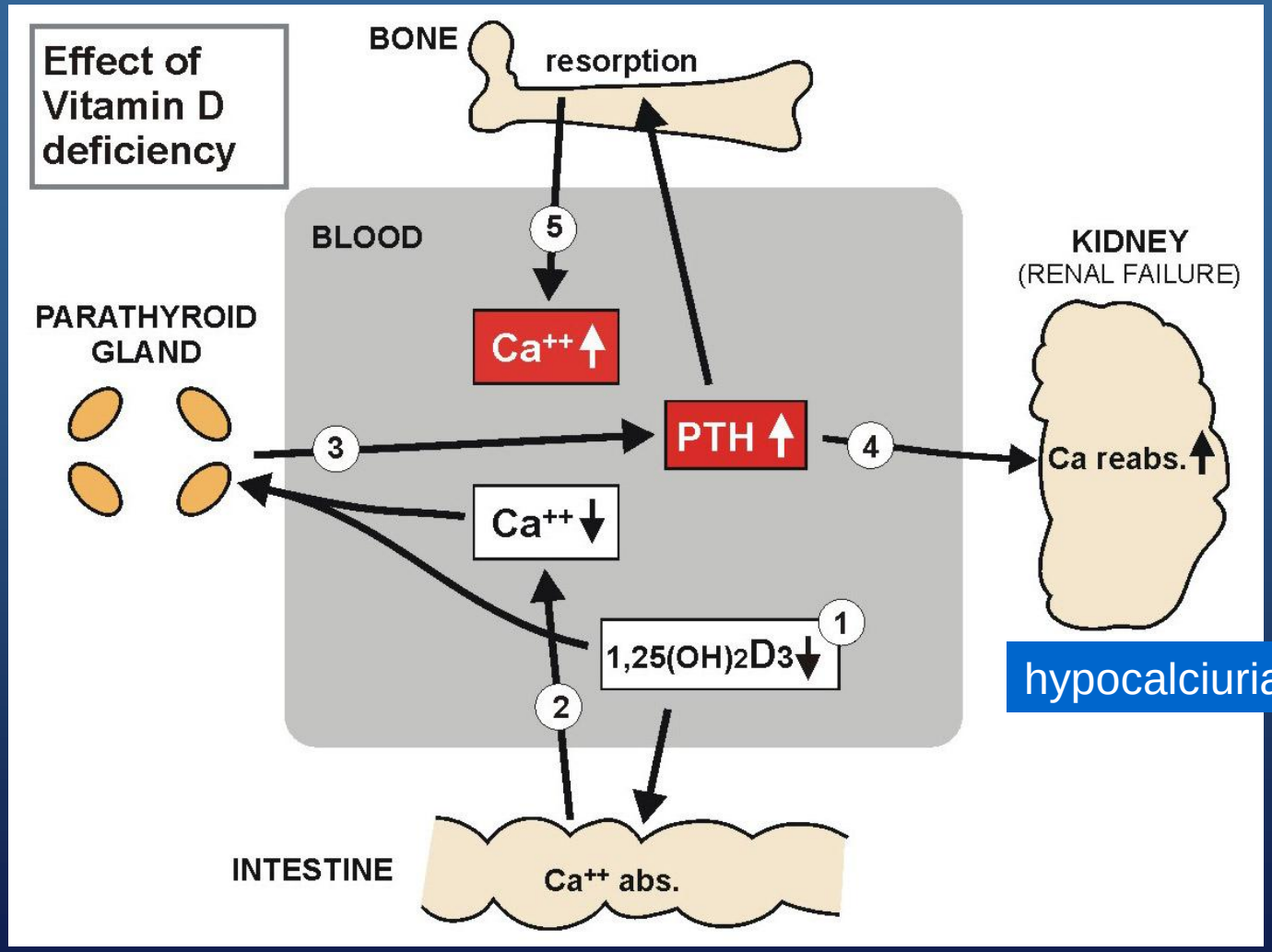


1. CASR cell suface G protein – coupled receptor ;extrac. Ca^{++}
2. Vitamin D receptor nuclear receptor controlling gene transcription
3. Uncharacterized phosphate sensor
4. FGF23 is a negative regulator of parathyroid function

Universiteit Antwerpen

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

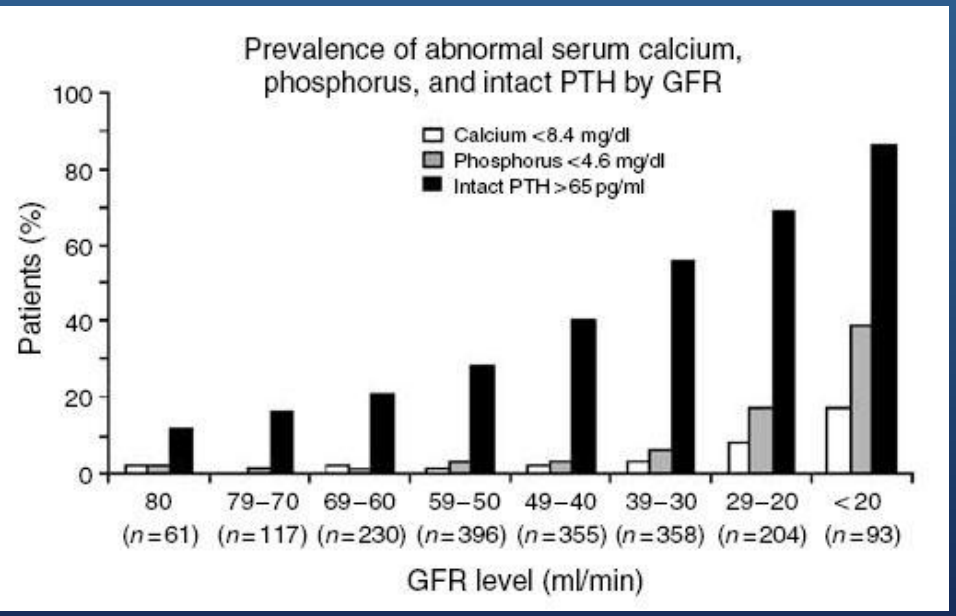
Consequences of phosphate accumulation in CRF

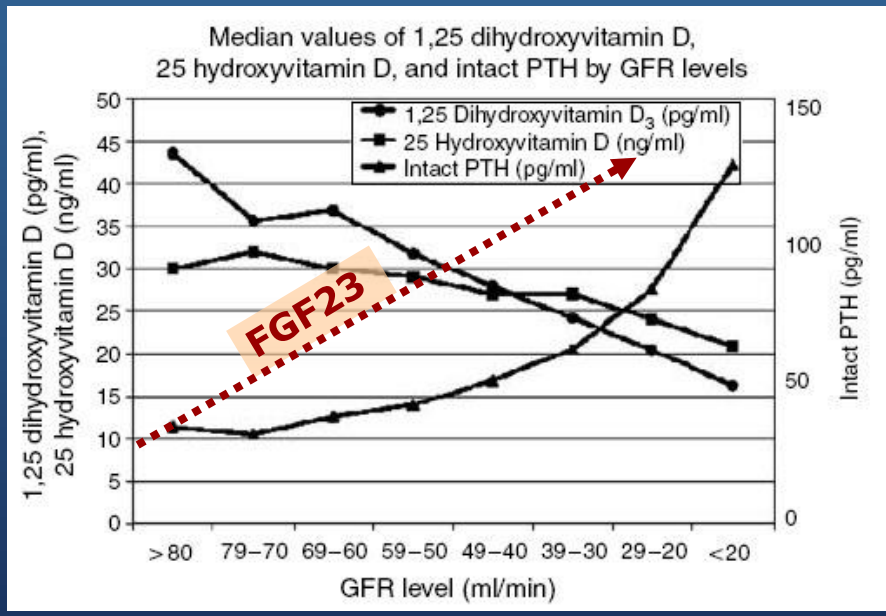


Behets G, PhD thesis, 2005

DDW3398

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*





Decrease in Vit D receptors
Decrease in Ca sensing receptors on PTH gland

Early increase of FGF23
No relation to the renal mass
Hypocalciuria
Tendency to hypocalcemia

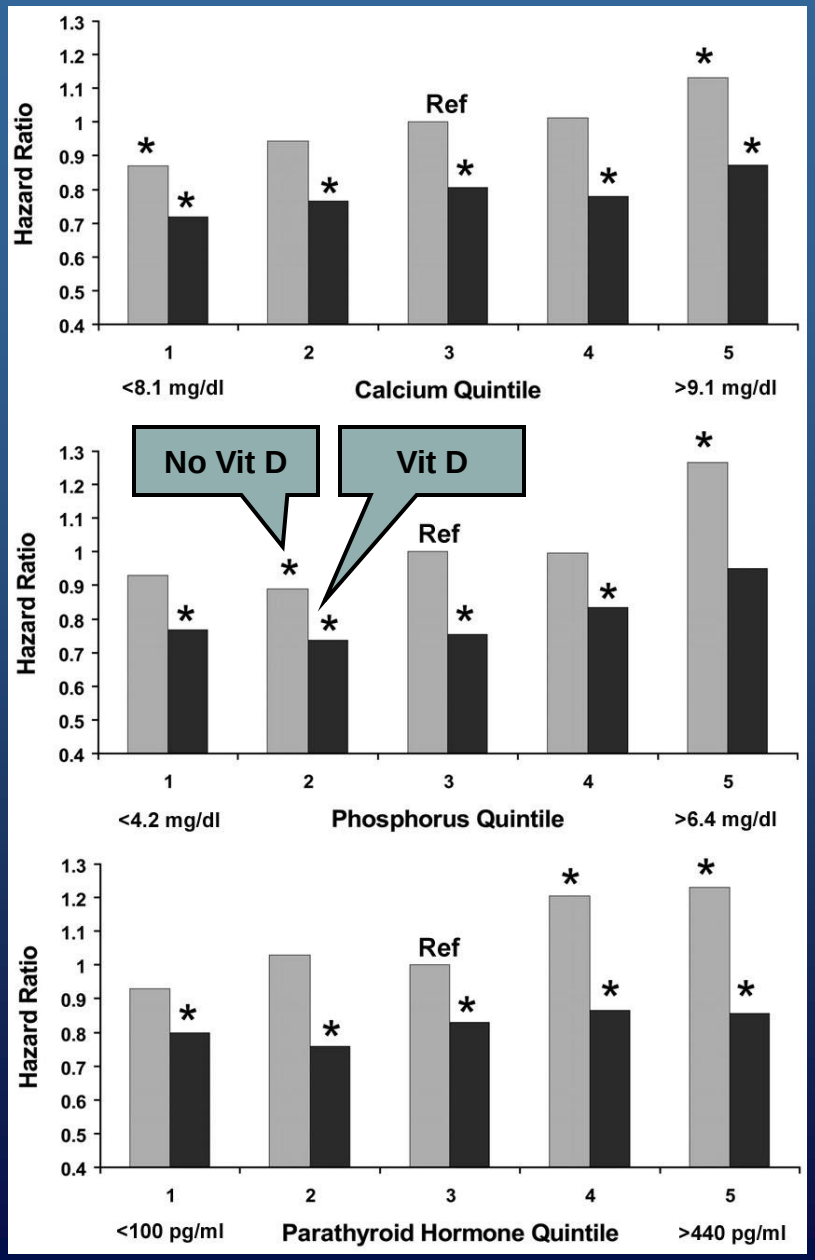
2

SECUNDARY HYPERPARATHYROIDISM

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

Activated injectable vitamin D and hemodialysis survival:

A historical cohort study

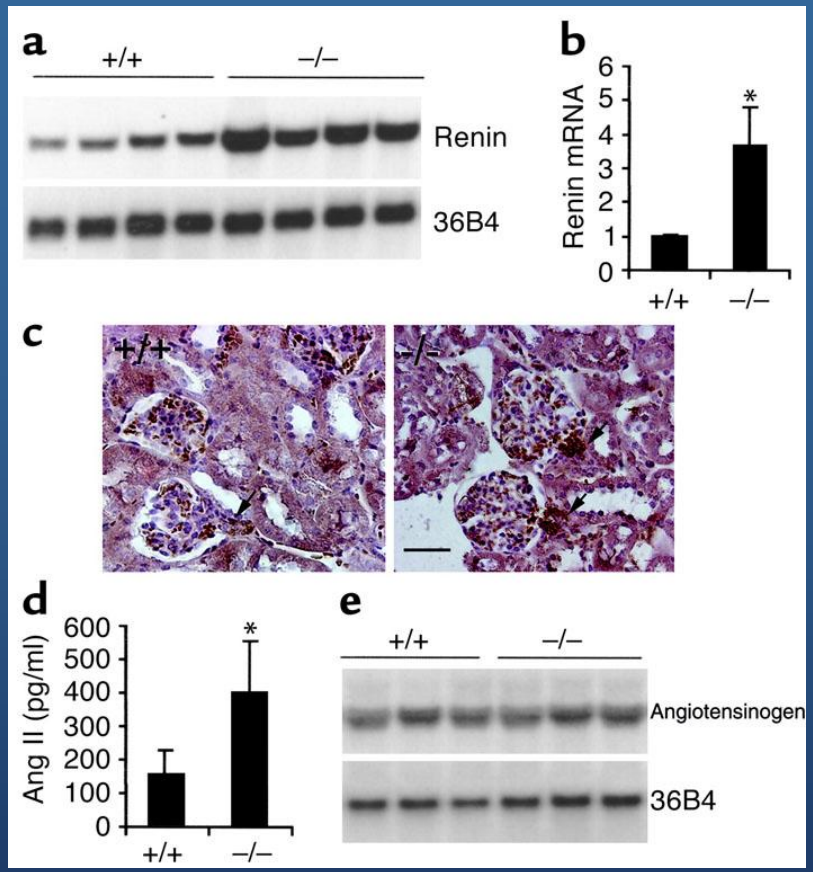


Teng M et al, J Am Soc Nephrol 16: 1115-1125, 2005

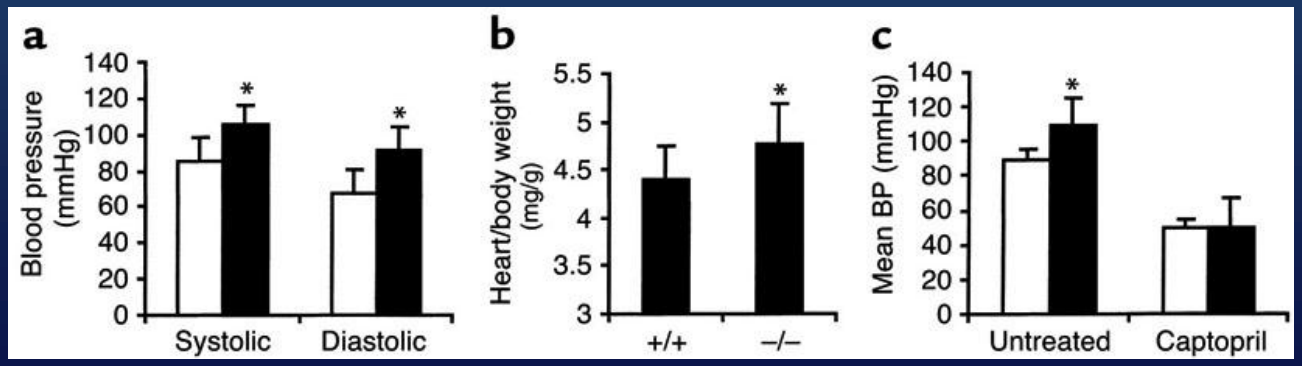
DDW3569

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



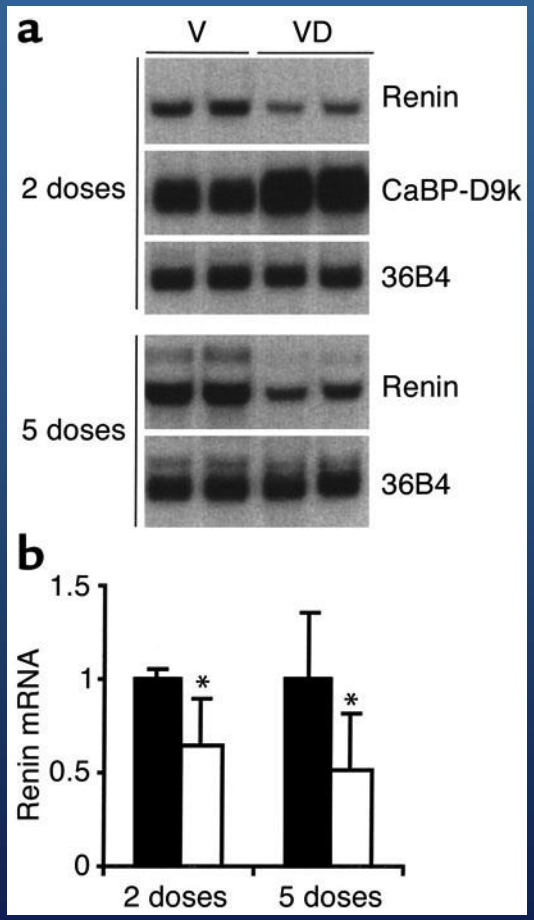
Effect of VDR inactivation on blood pressure and heart weight/body weight ratio



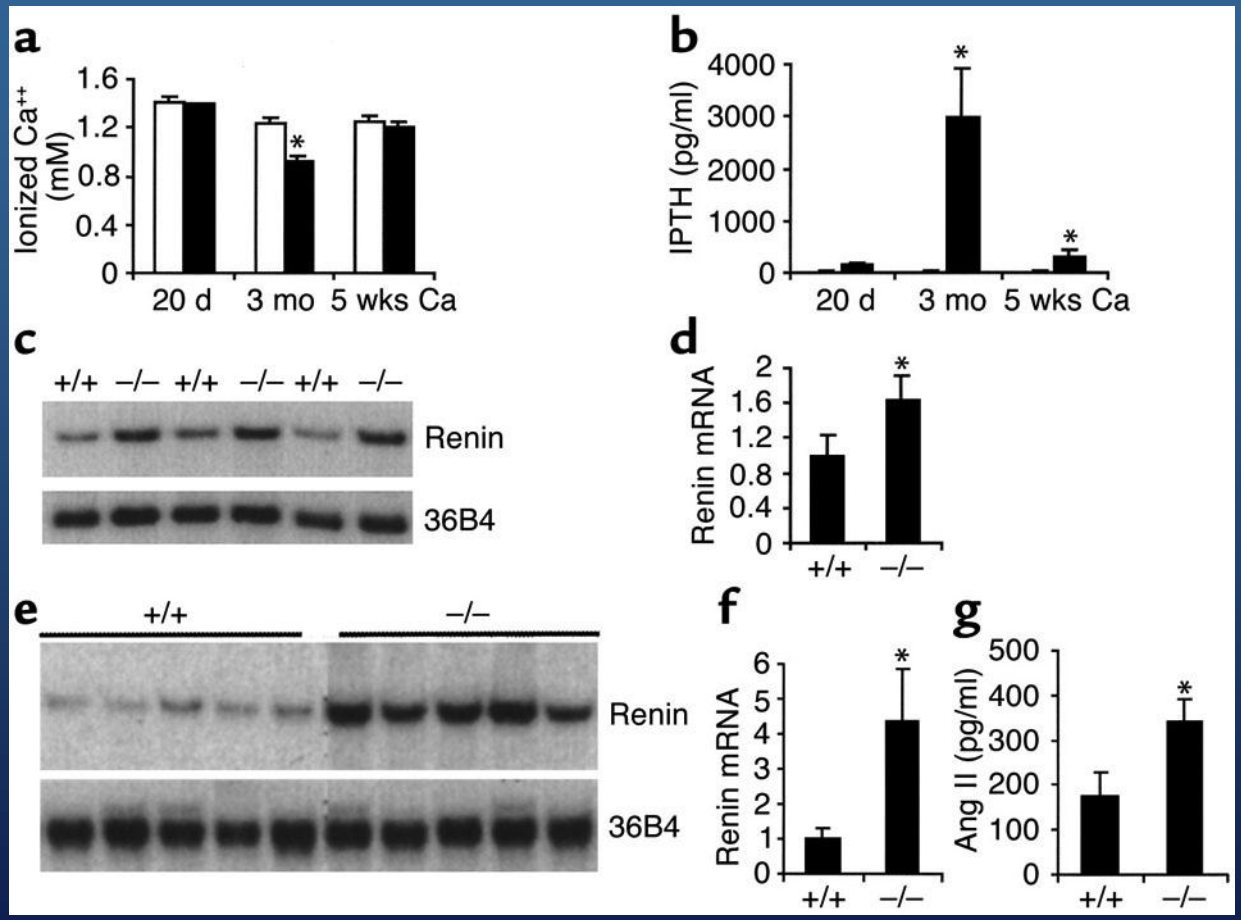
Li YC et al: JCI 110: 229-238, 2002

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



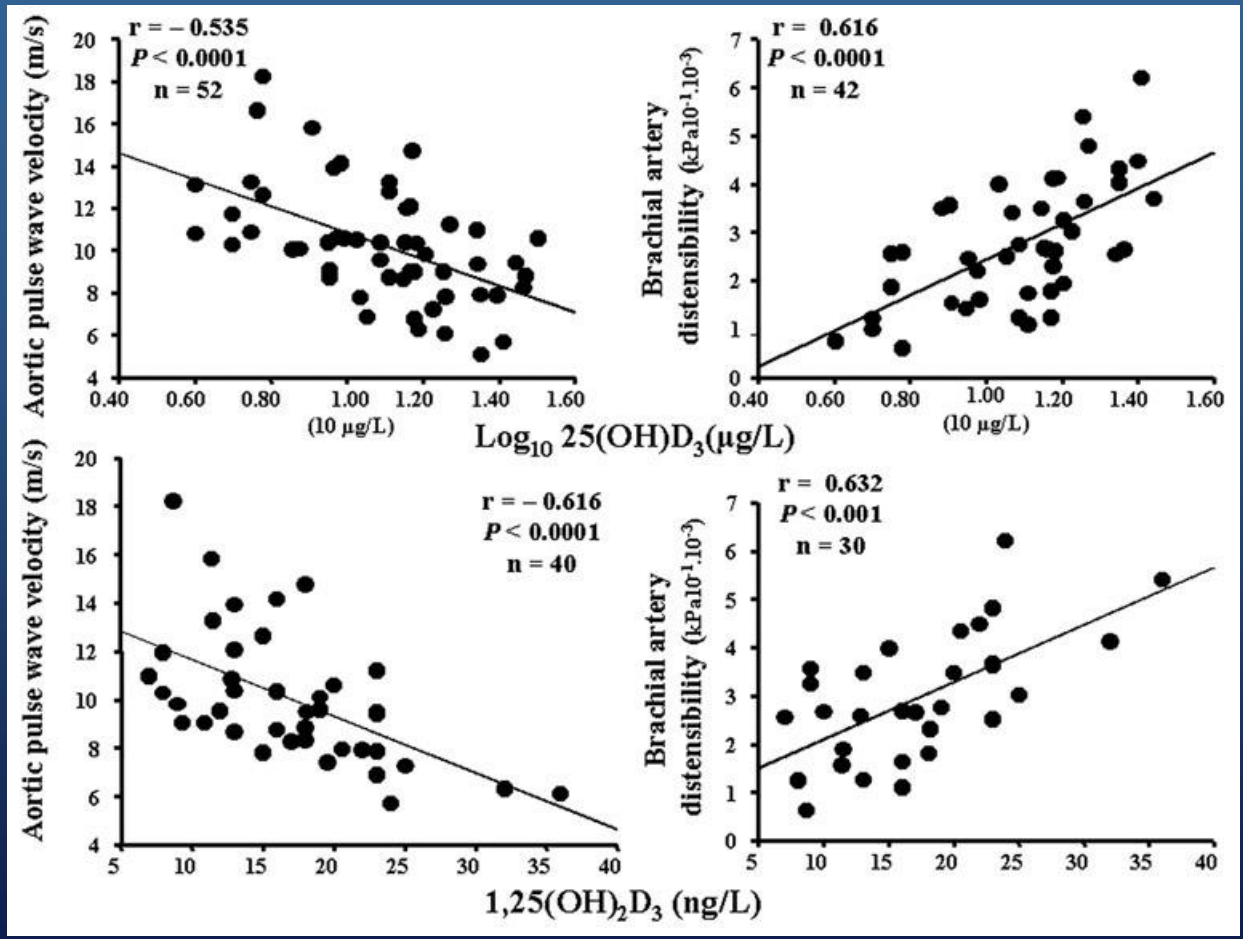
Renin upregulation is independent of the calcium status

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

DDW3566

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

CUSHIONING FUNCTION
dampen blood flow pressure oscillations

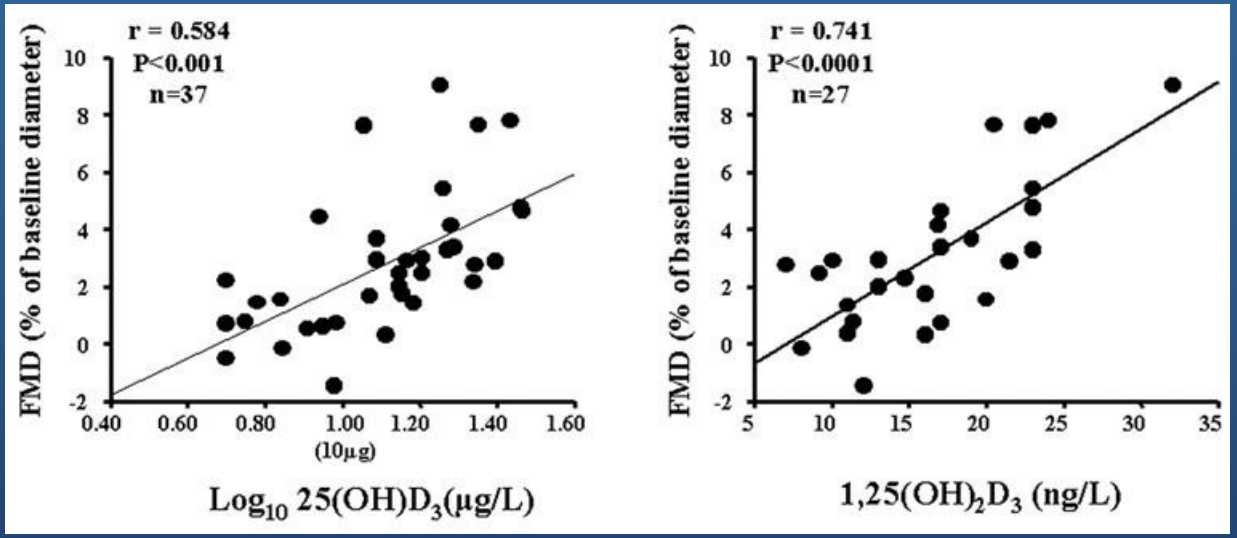


London GM et al, JASN 18: 613-620, 2007

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

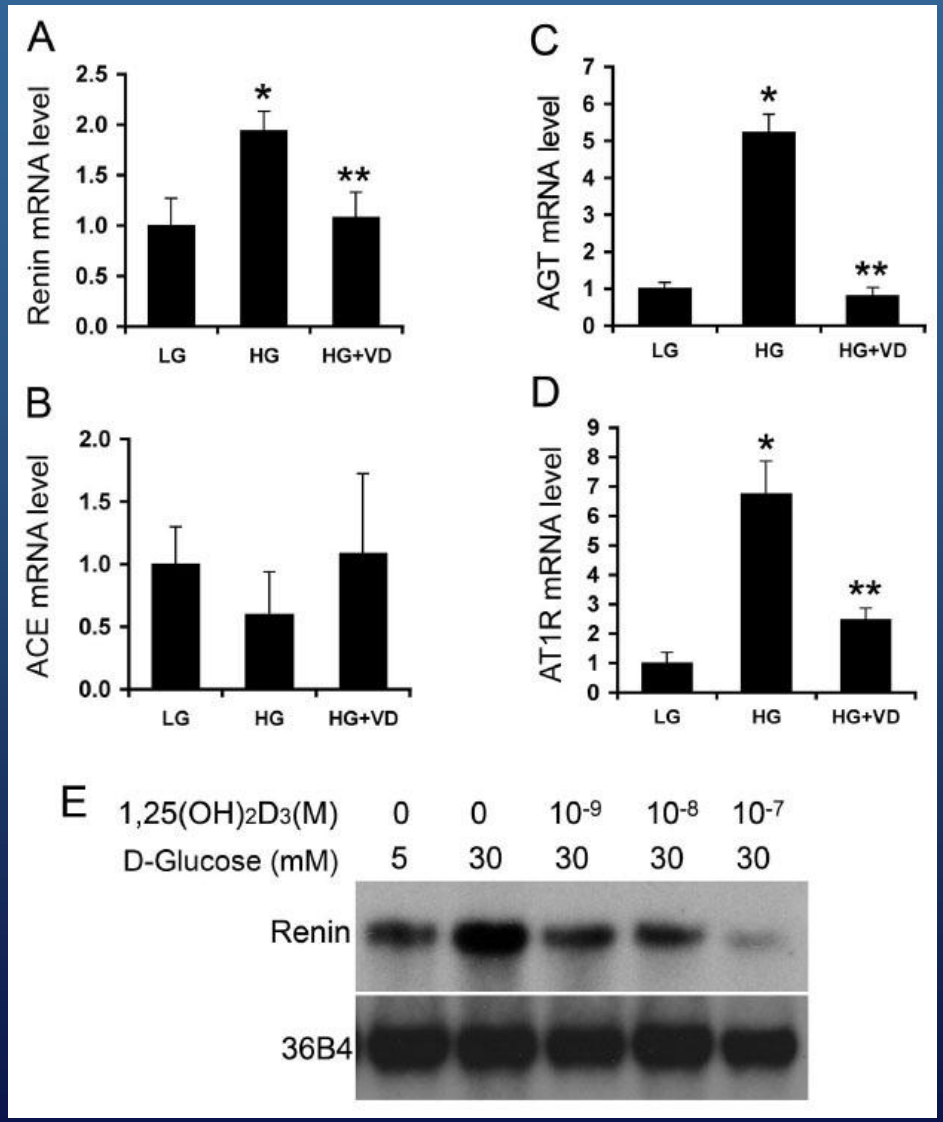
London GM et al, JASN 18: 613-620, 2007

FMD flow mediated dilation

DDW3569

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

Effect of vitamin D on RAS expression in mesangial and JG cells.

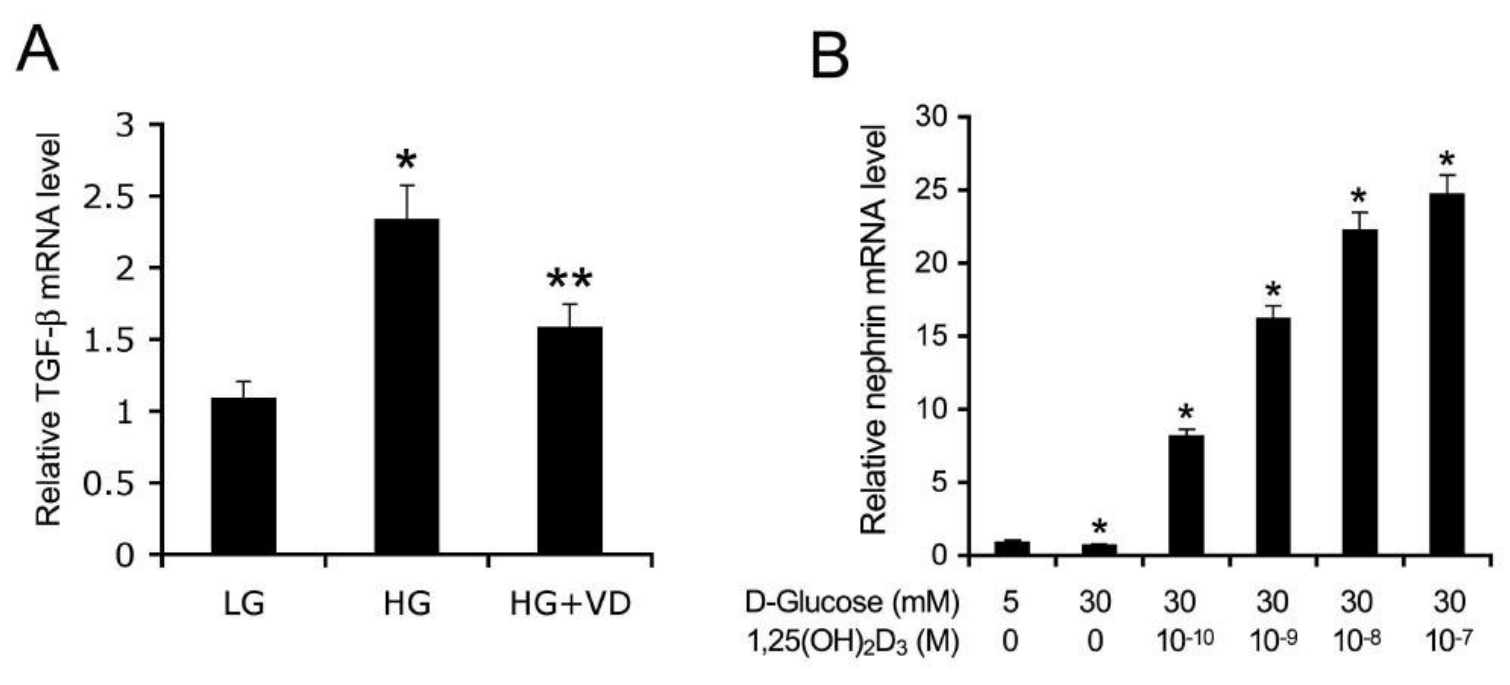


* P<0.05 vs. low glucose (LG)
* P<0.05 vs. high glucose (HG)

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

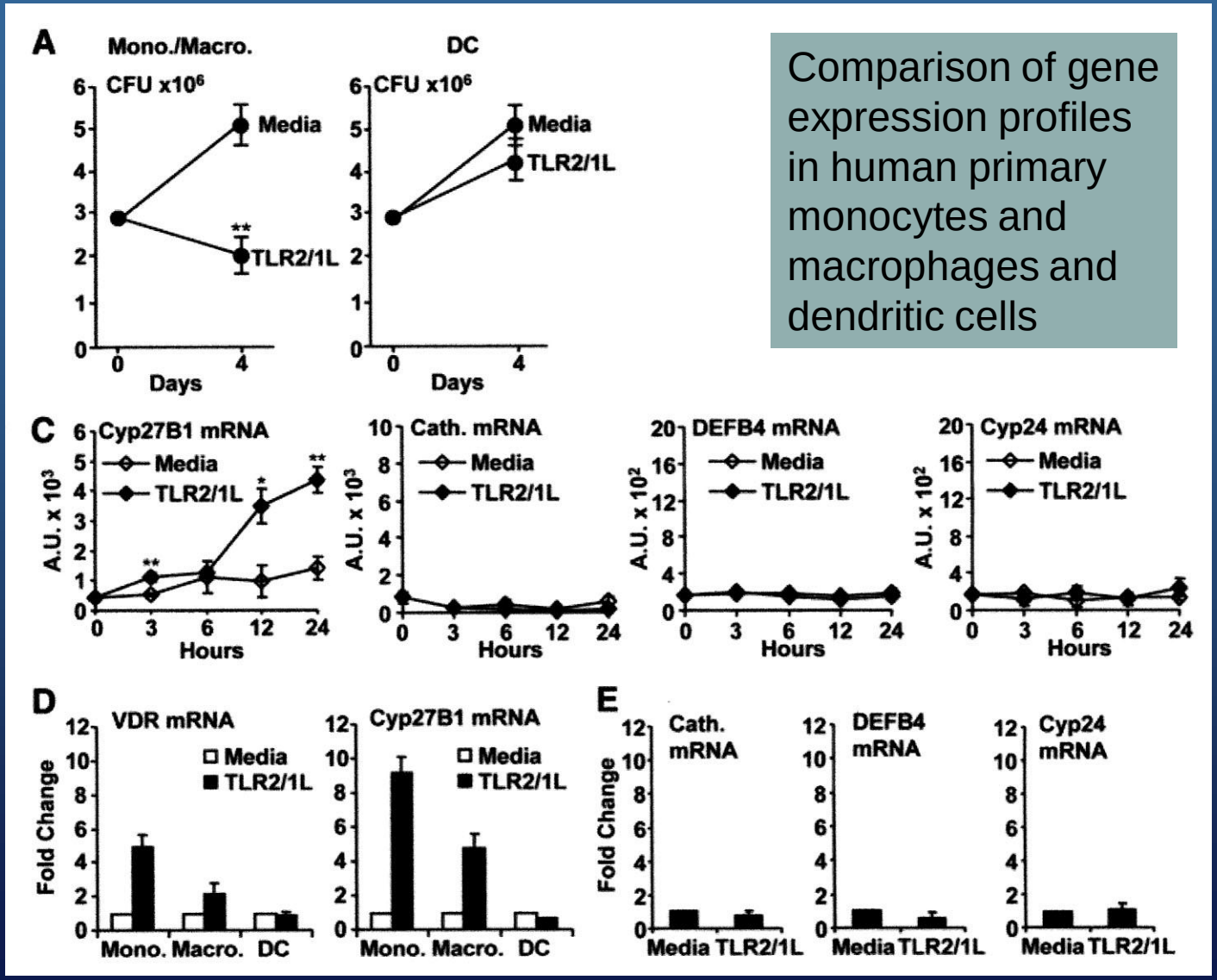
DDW3607

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

Infected cells
Myc Tuberc.

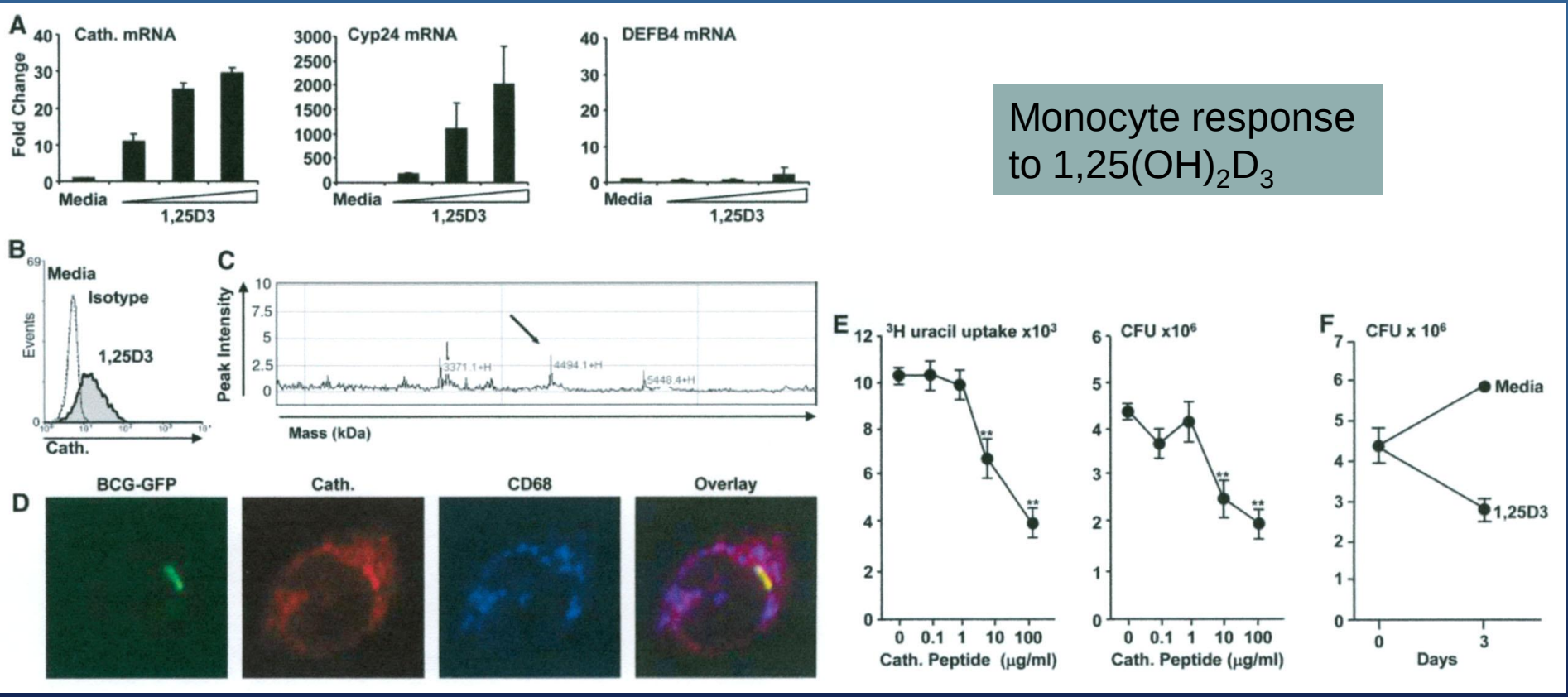
TLR2/1L :
Ligand: Mycob Tuberc derived peptide

Reduced viability



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

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

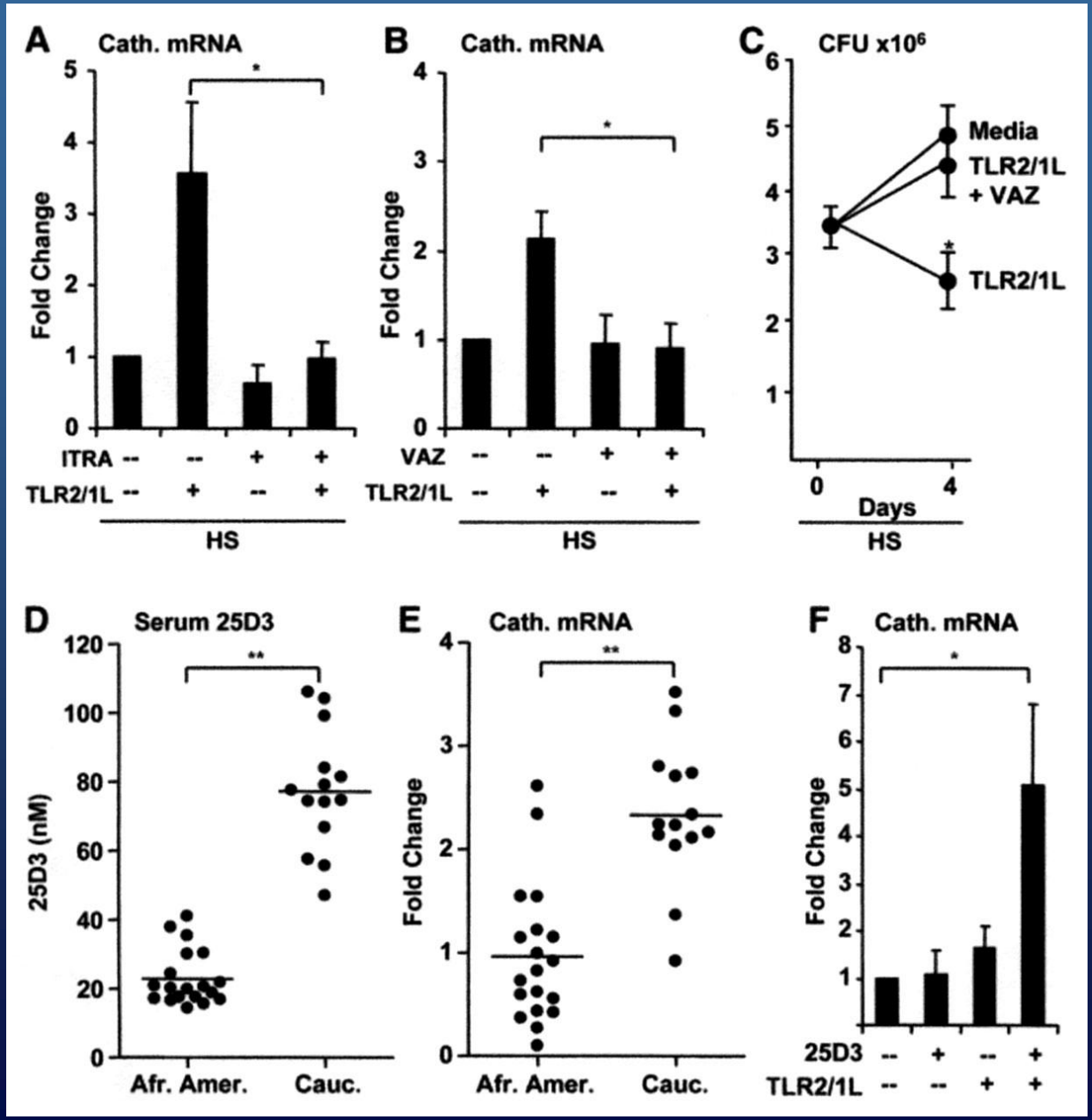
Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response

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

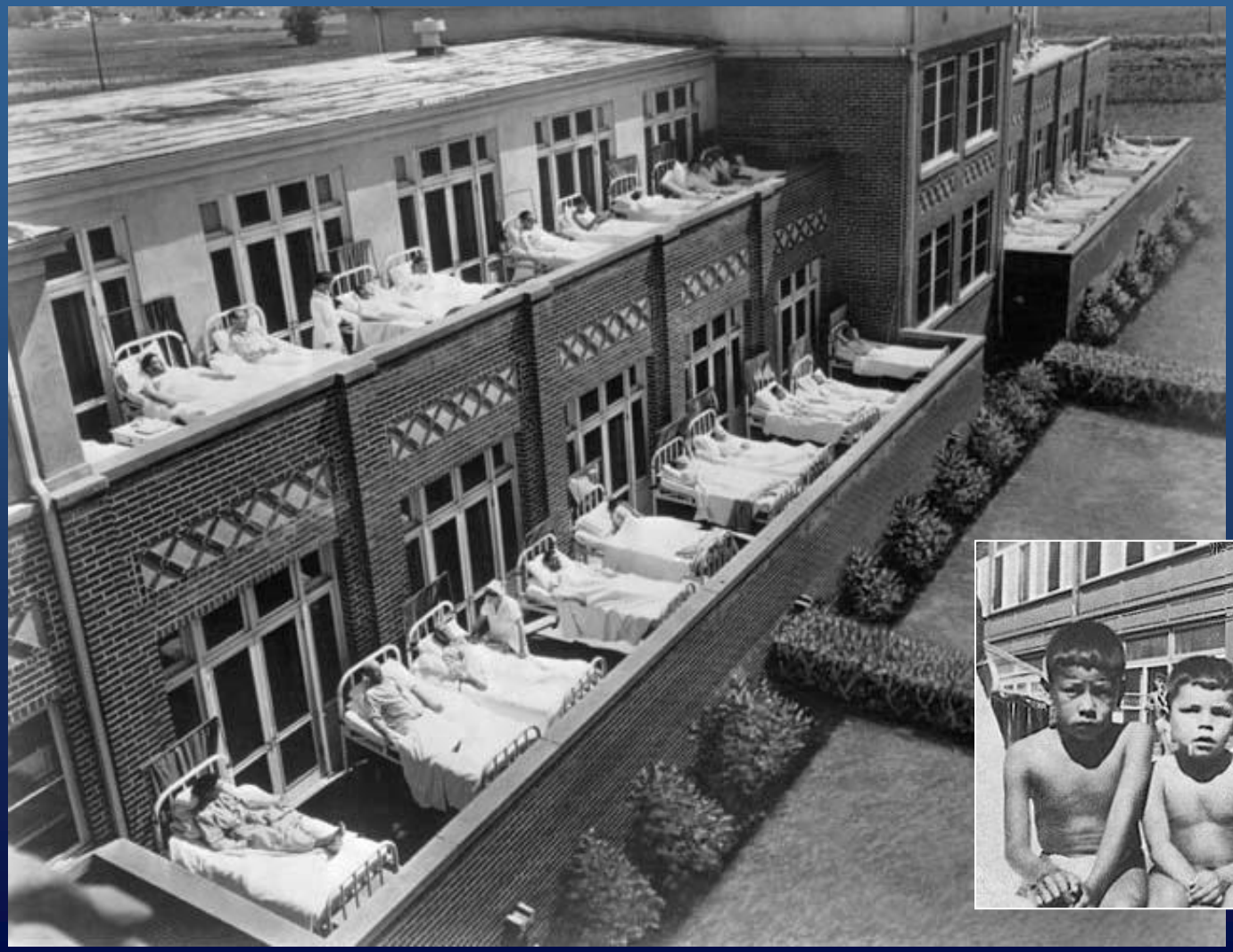


Liu PT et al: Science 311: 1770-3, 2006

DDW3576

Sunlight treatment for tuberculosis

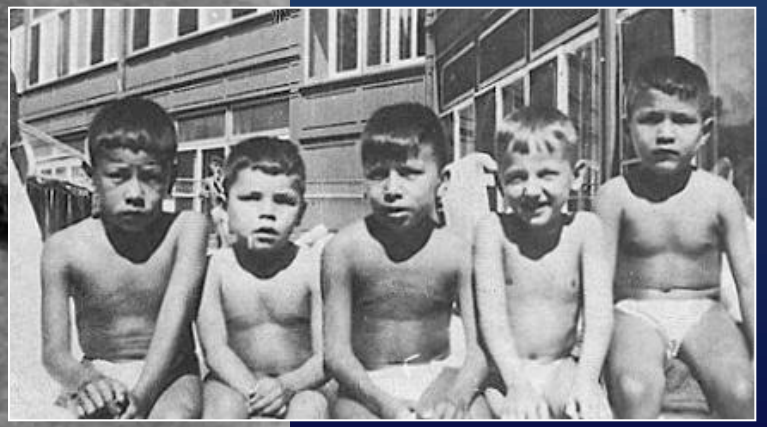
Brehmer & Trudeau



Niels Ryberg Finsen

Denmark

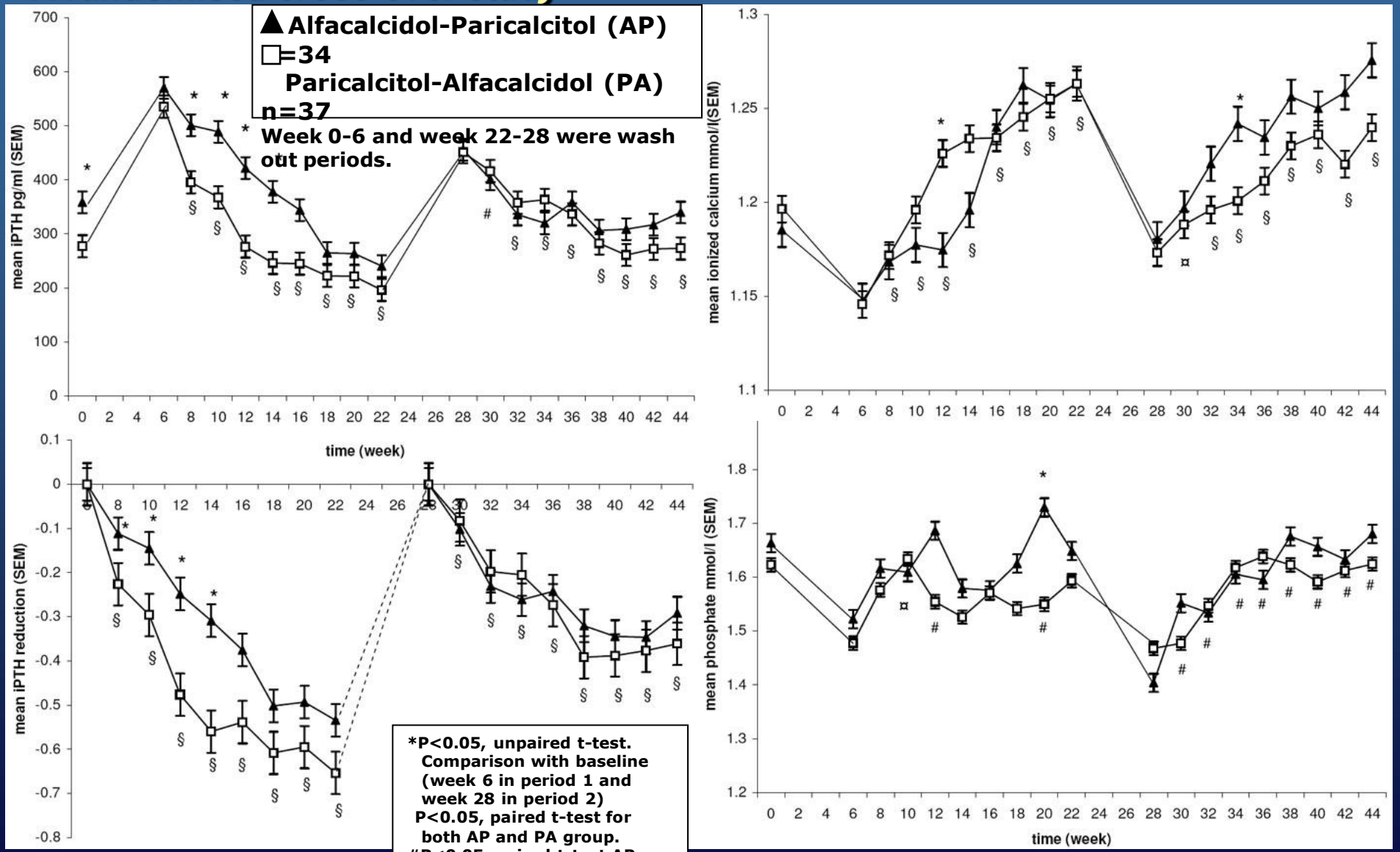
Nobel Prize 1903



DDW3655

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

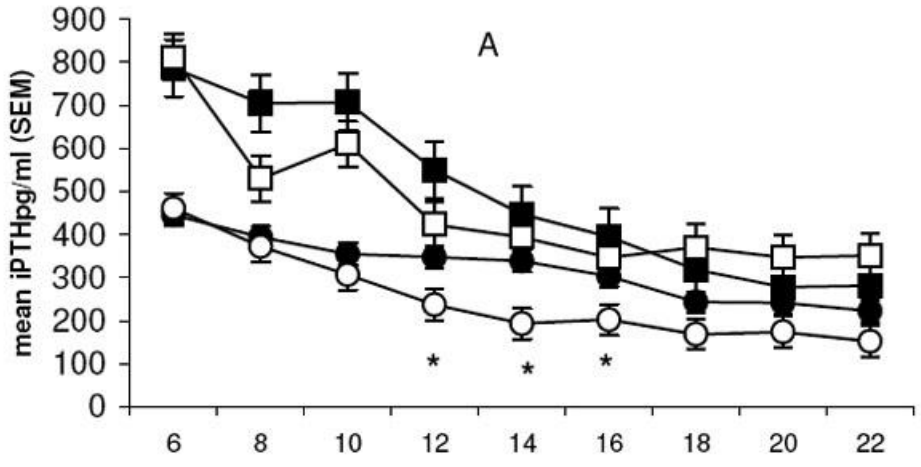
A randomised cross-over study

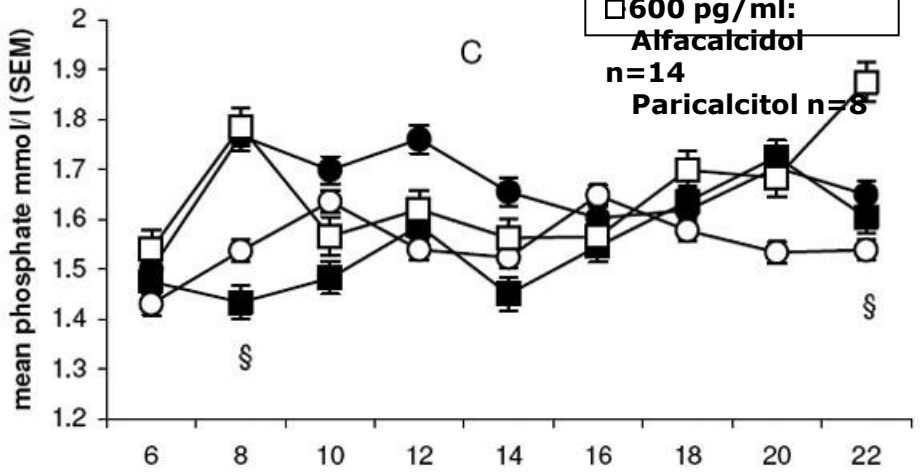


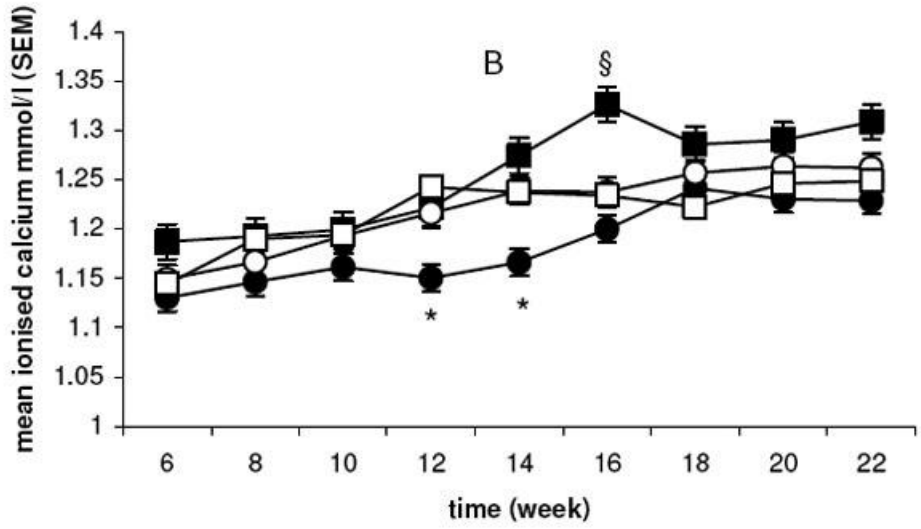
Hansen D et al: Kidney Int 2011 (In press)

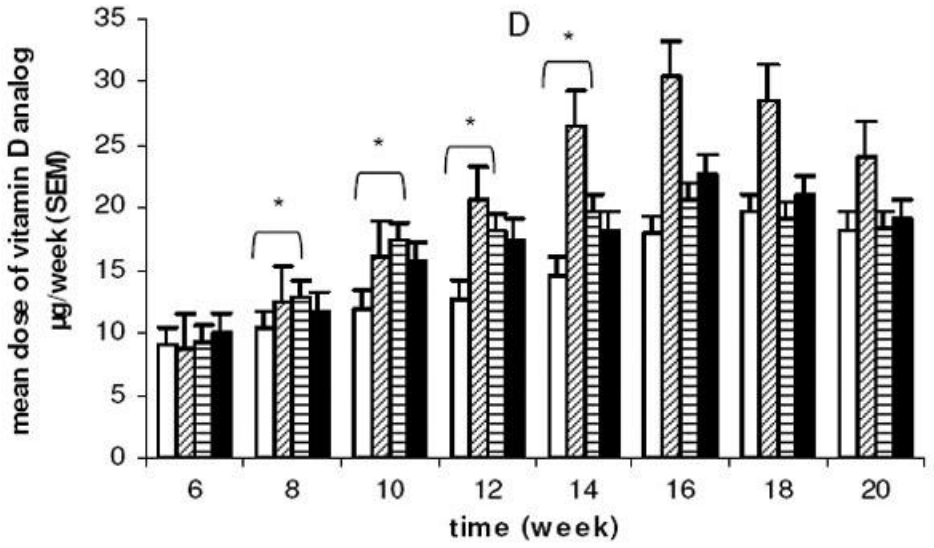
Comparison of alfacalcidol and paricalcitol for treatment of secondary hyperparathyroidism in hemodialysis patients.
A randomised cross-over study

Low baseline PTH ≤ 600 pg/ml:
●Alfacalcidol ○=24
Paricalcitol n=34
■igh baseline PTH □600 pg/ml:
Alfacalcidol n=14
Paricalcitol n=8









*P<0.05 and high PTH groups P<0.05 (unpaired t-test)

Hansen D et al:
Kidney Int 2011 (In press)

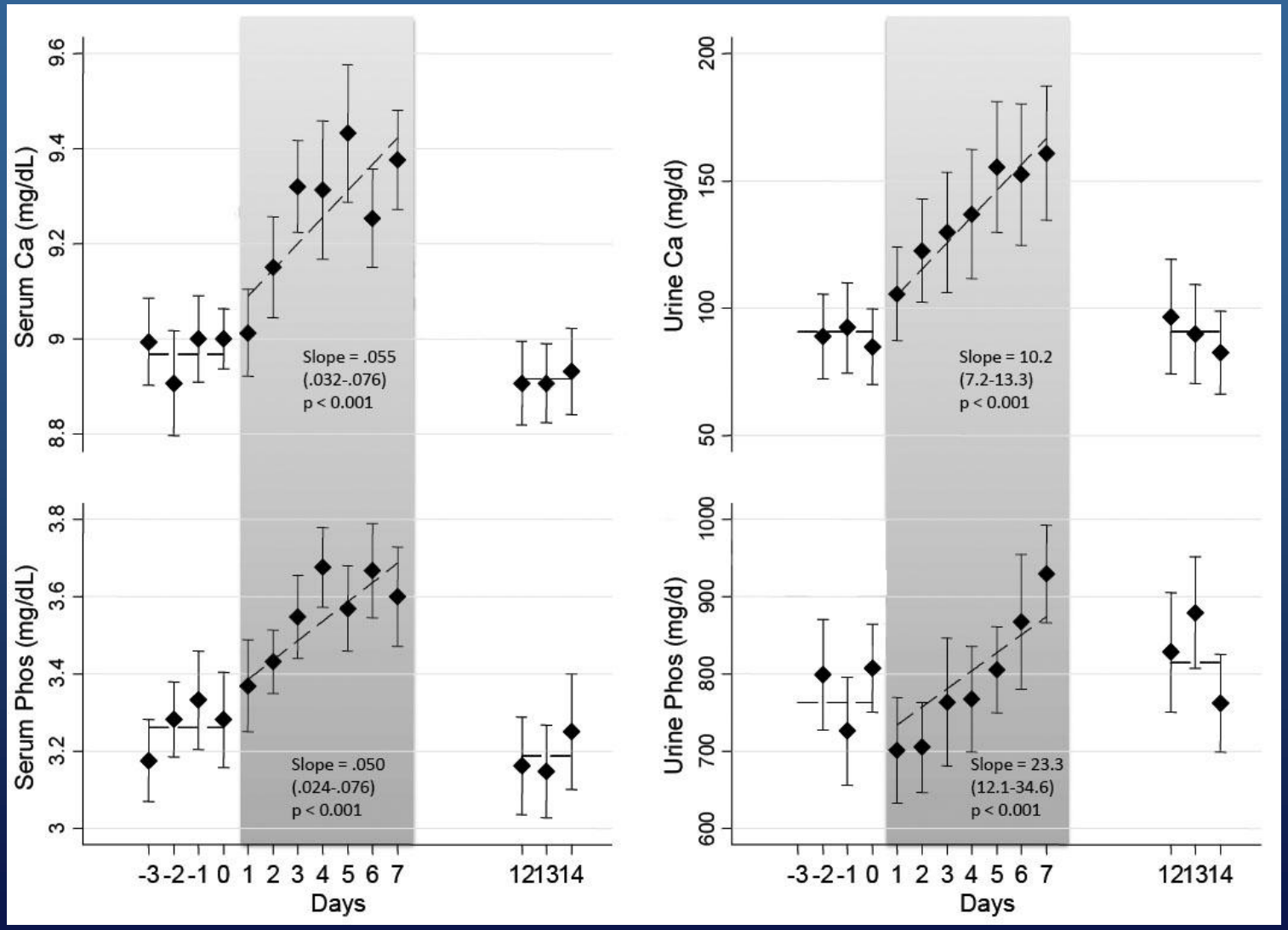
Comparison of alfacalcidol and paricalcitol for treatment of secondary hyperparathyroidism in hemodialysis patients.
A randomised cross-over study

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

	Number (%) of patients		P-value
	Alfacalcidol n=38	Paricalcitol n=42	
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

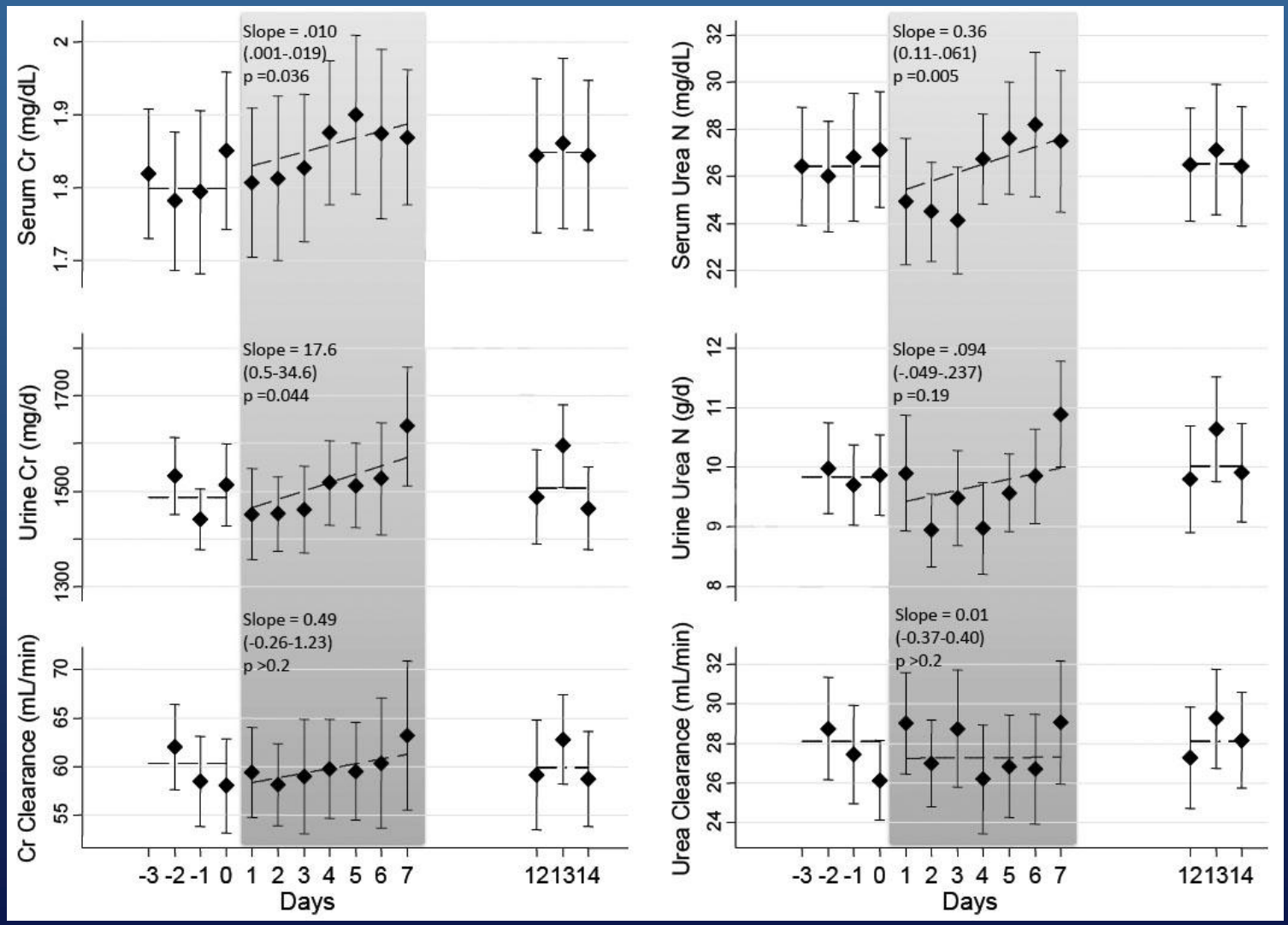
Hansen D et al:
Kidney Int 2011 (In press)

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)

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



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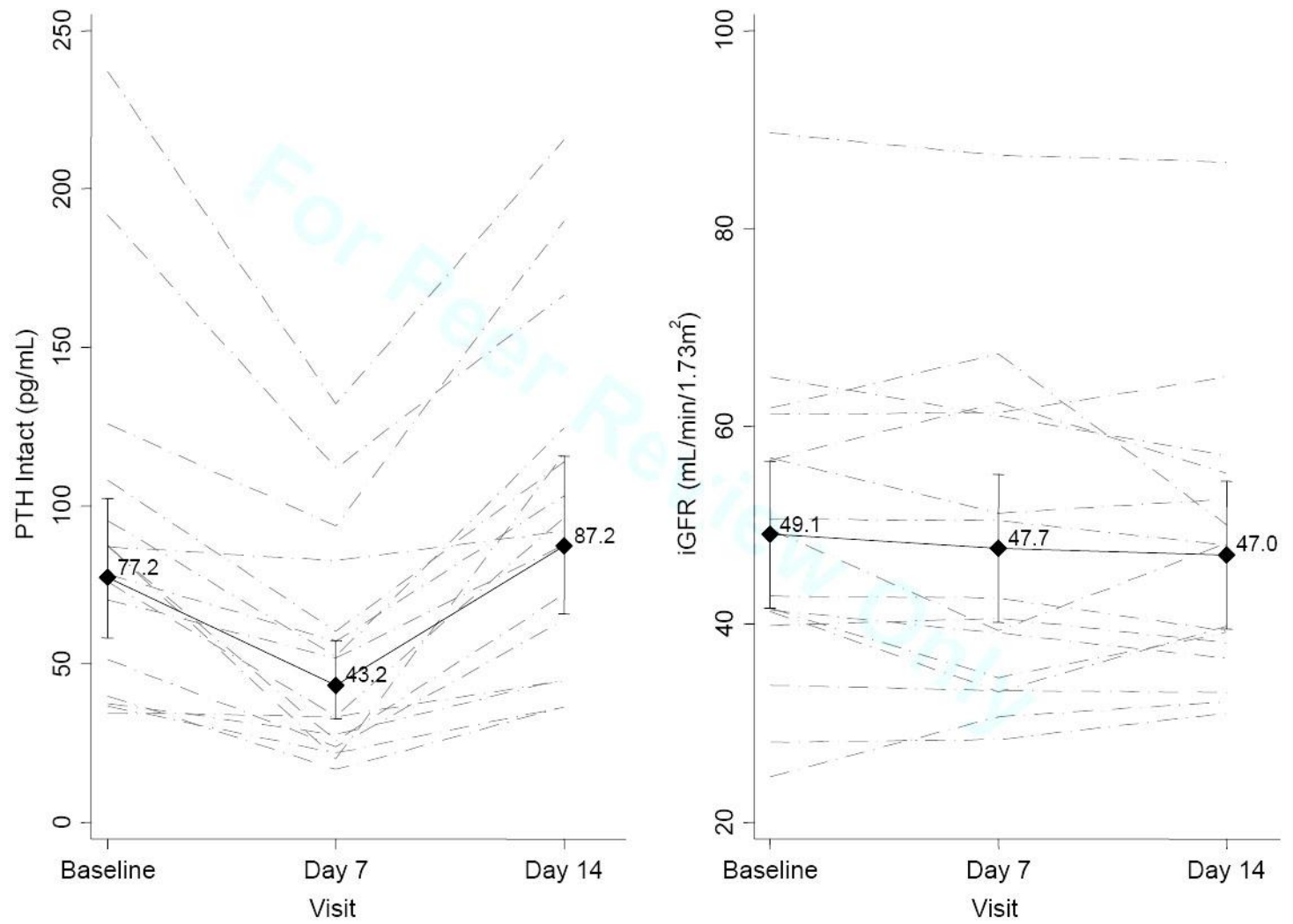
Short-term effects of vitamin D receptor activation on serum creatinine, creatinine generation, and glomerular filtration rate



For Peer Review Only

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

HOW TO SUPPLEMENT ?

Recommended blood concentrations

Taux inadéquats : supplémentation nécessaire

25 OH vitamine D	nmol/L	ng/mL
Deficiency (1)	**< 25**	**< 10**
Insufficiency (2)	**25 - 75**	**10 - 30**
Aim (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.

Available Native Vitamin 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.

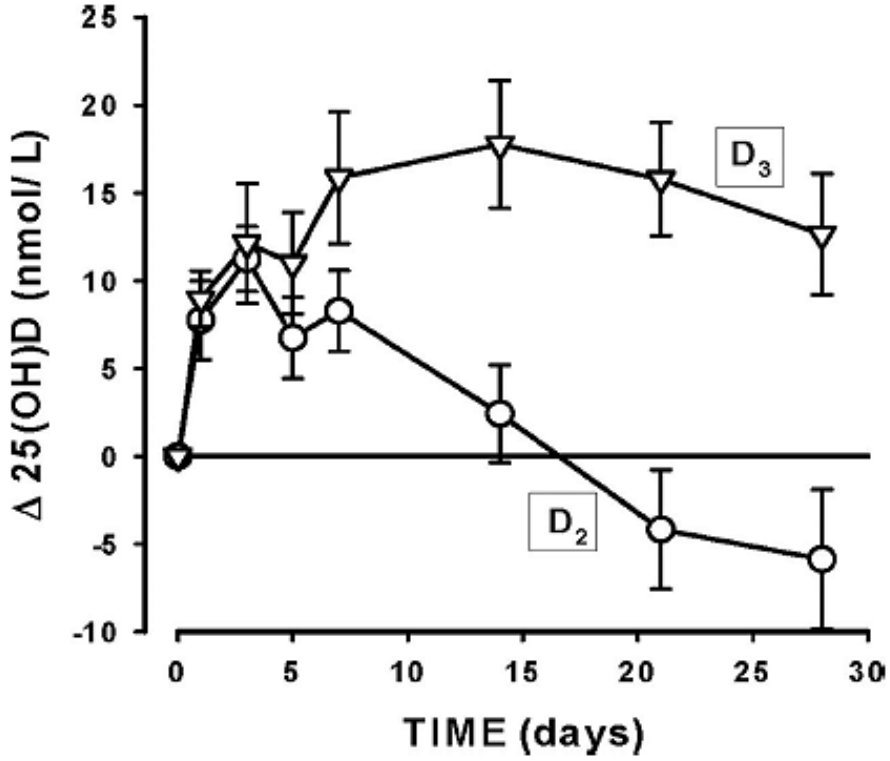
Posologies

(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

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



La D2 a une ½ vie plus courte que la D3

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 100 000 mensuel en dialyse

G Jean et al,NDT(2009) 24: 3799–3805

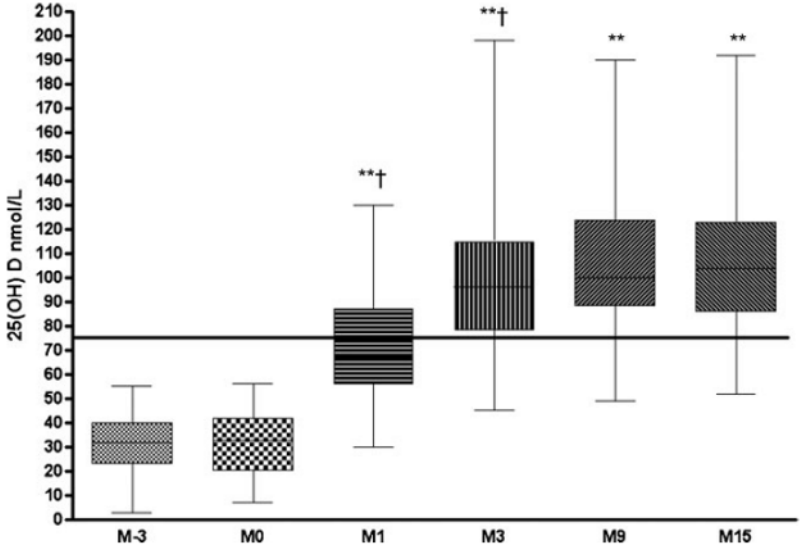


Fig. 1. Evolution of 25(OH)D serum levels (Box plot). $^{**}P < 0.001$ with baseline, $^{\dagger}P < 0.05$ with the previous value.

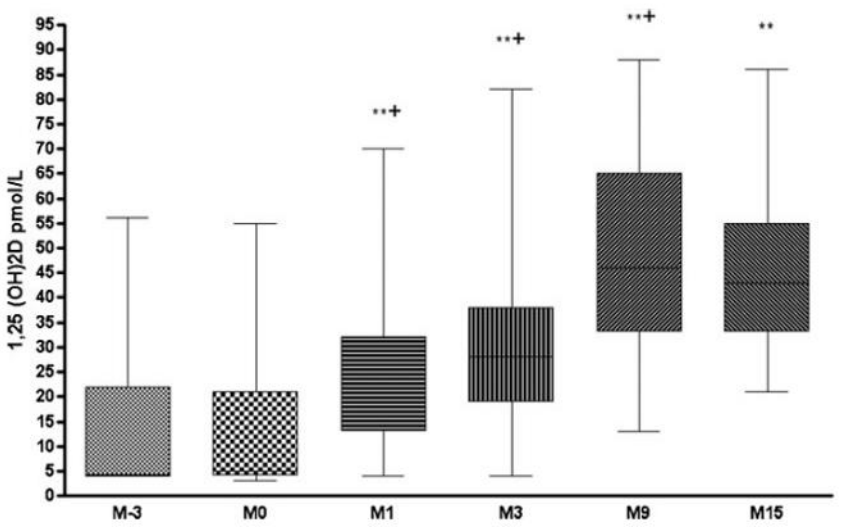


Fig. 2. Evolution of 1,25(OH)2D serum levels (Box plot). $^{**}P < 0.001$ with baseline, $^{\dagger}P < 0.05$ with the previous value.

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.

CONCLUSIONS: 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

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

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Conclusion

- **Vitamin D is an hormonal system controlling many genes**
- Many targets
- Favourable effect on survival
- Deficiency and insuffficiency in CKD
- 1 -alplha hydroxylase is ubiquitous
- substitution/supplementation using native
- Vitamin D

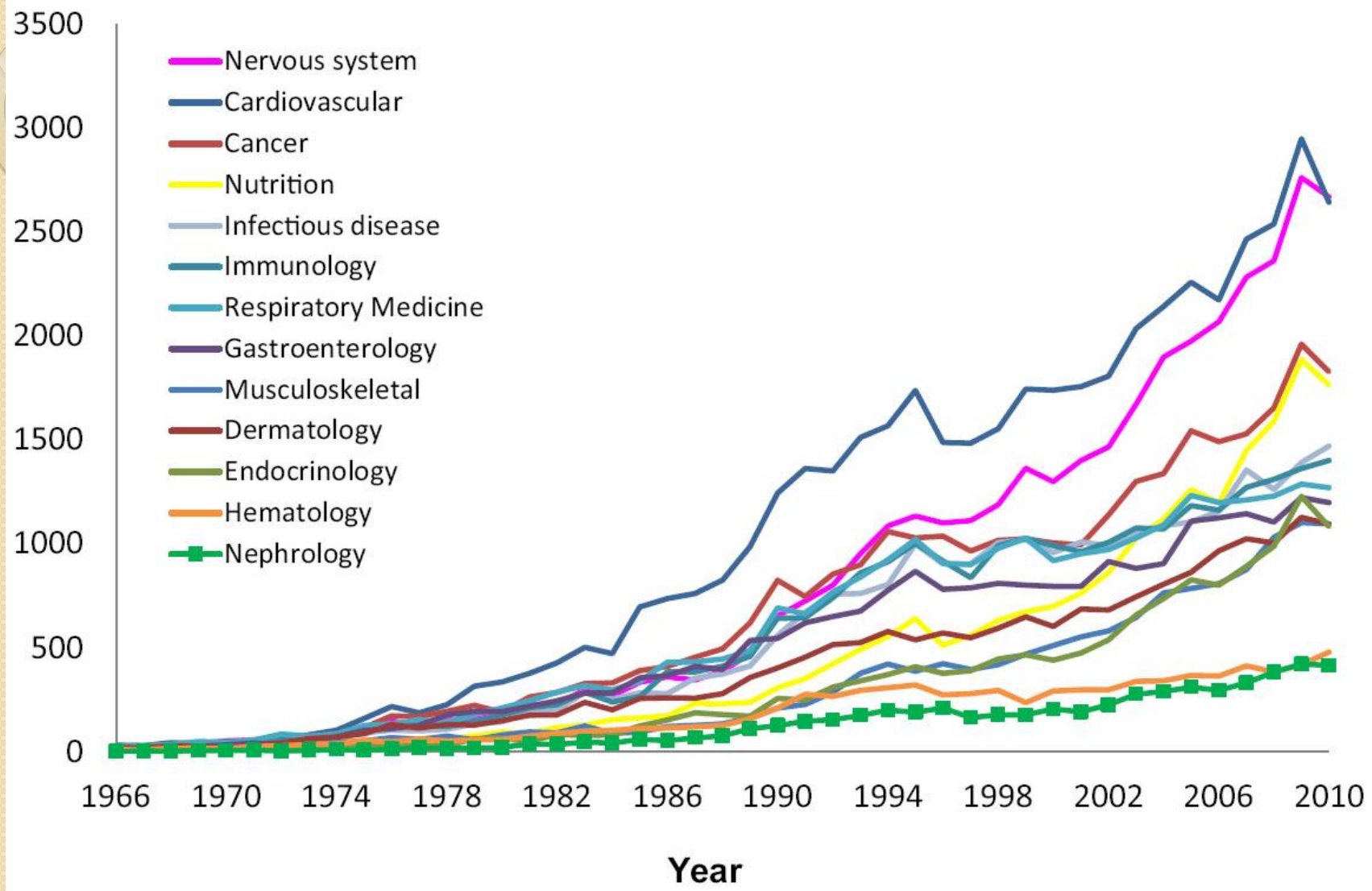
Apports alimentaires

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.

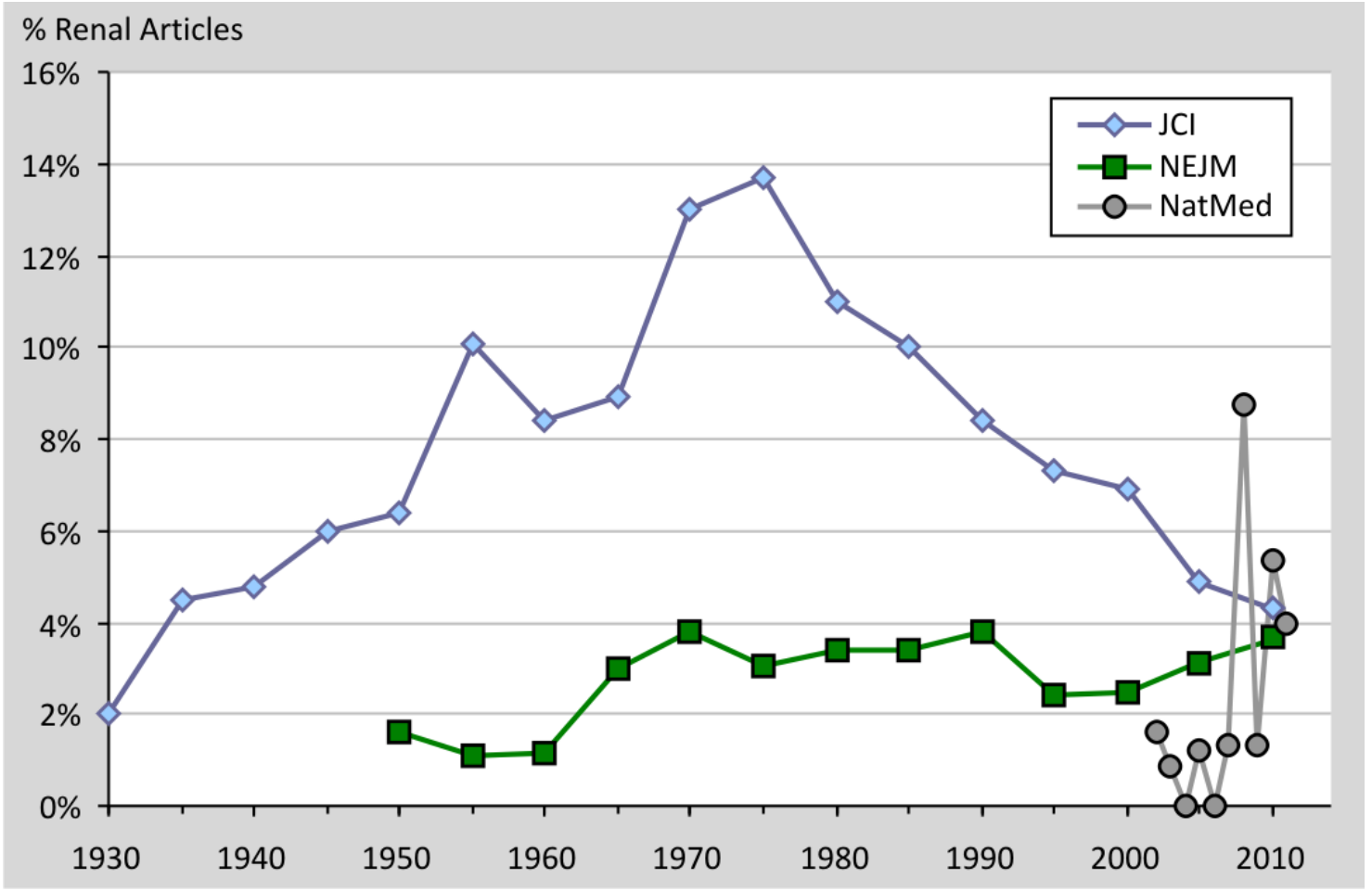
Trial quality in nephrology: how are we measuring up?



Palmer SC et al: Am J Kidney Dis 58:335-337, 2011

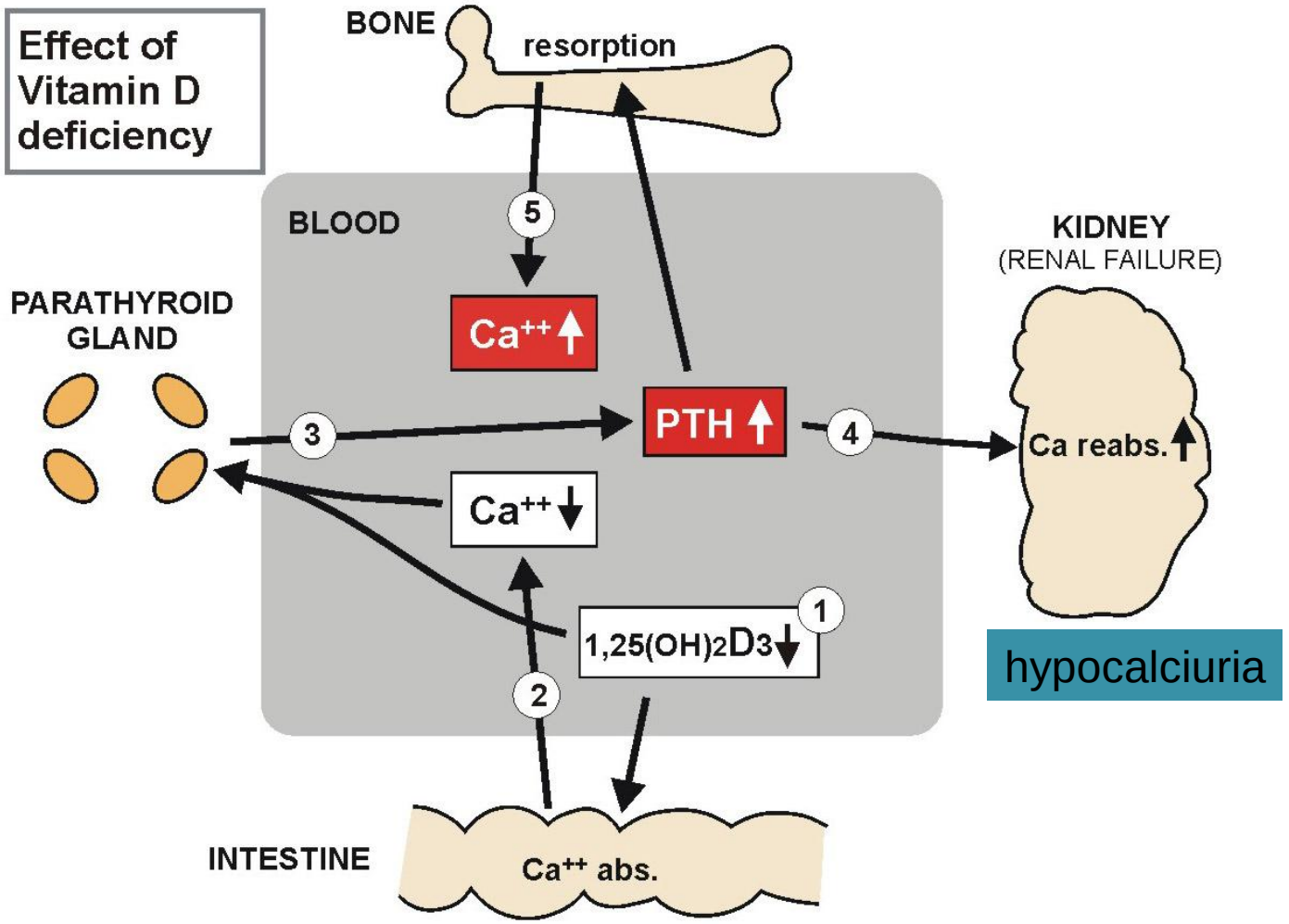
Renal articles in leading medical journals

- **Journal of Clinical Investigation**
- **New England Journal of Medicine**
- **Nature Medicine**



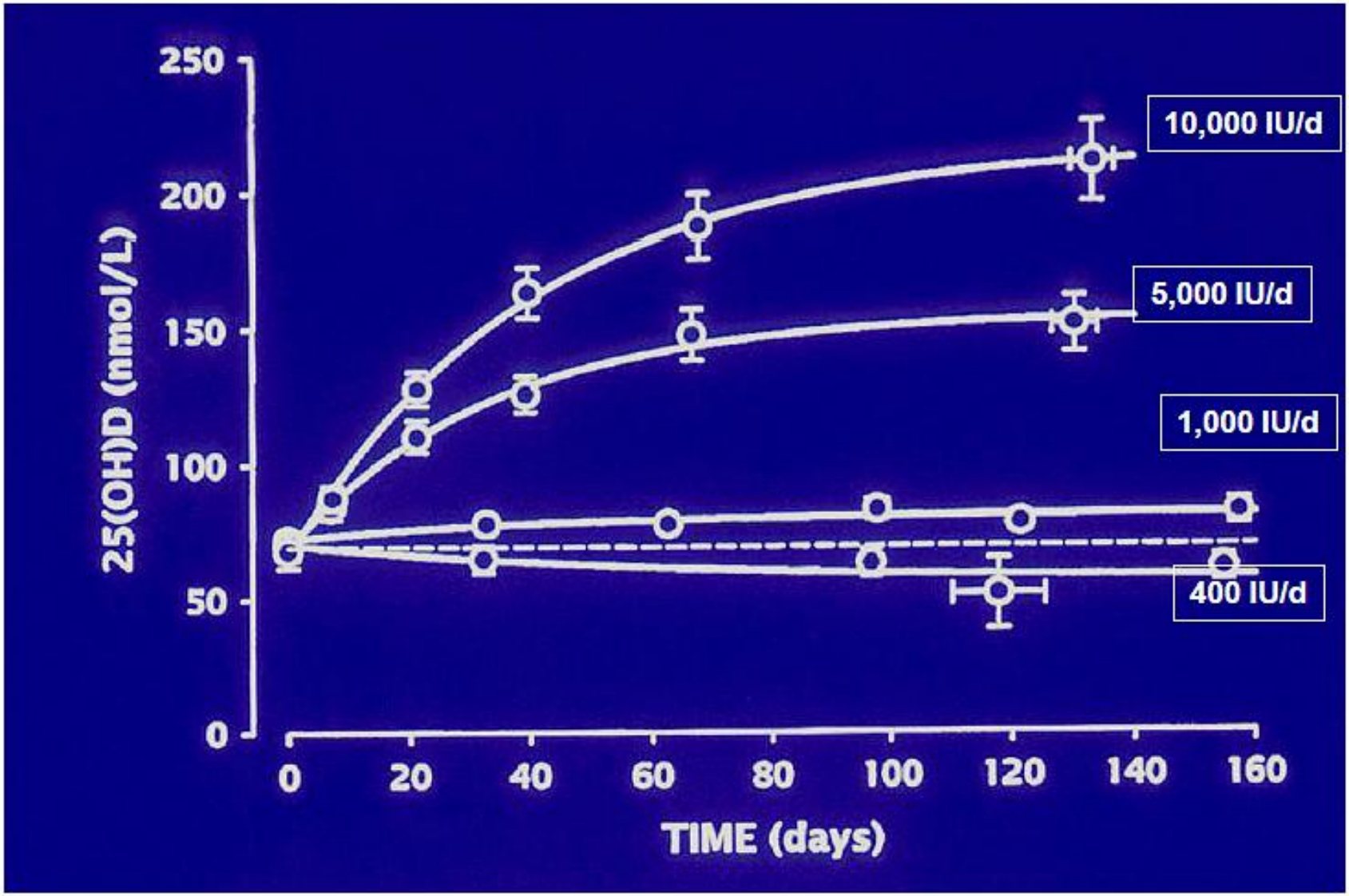
Al Quati Q, Snelders E, De Broe ME

Consequences of phosphate accumulation in CRF

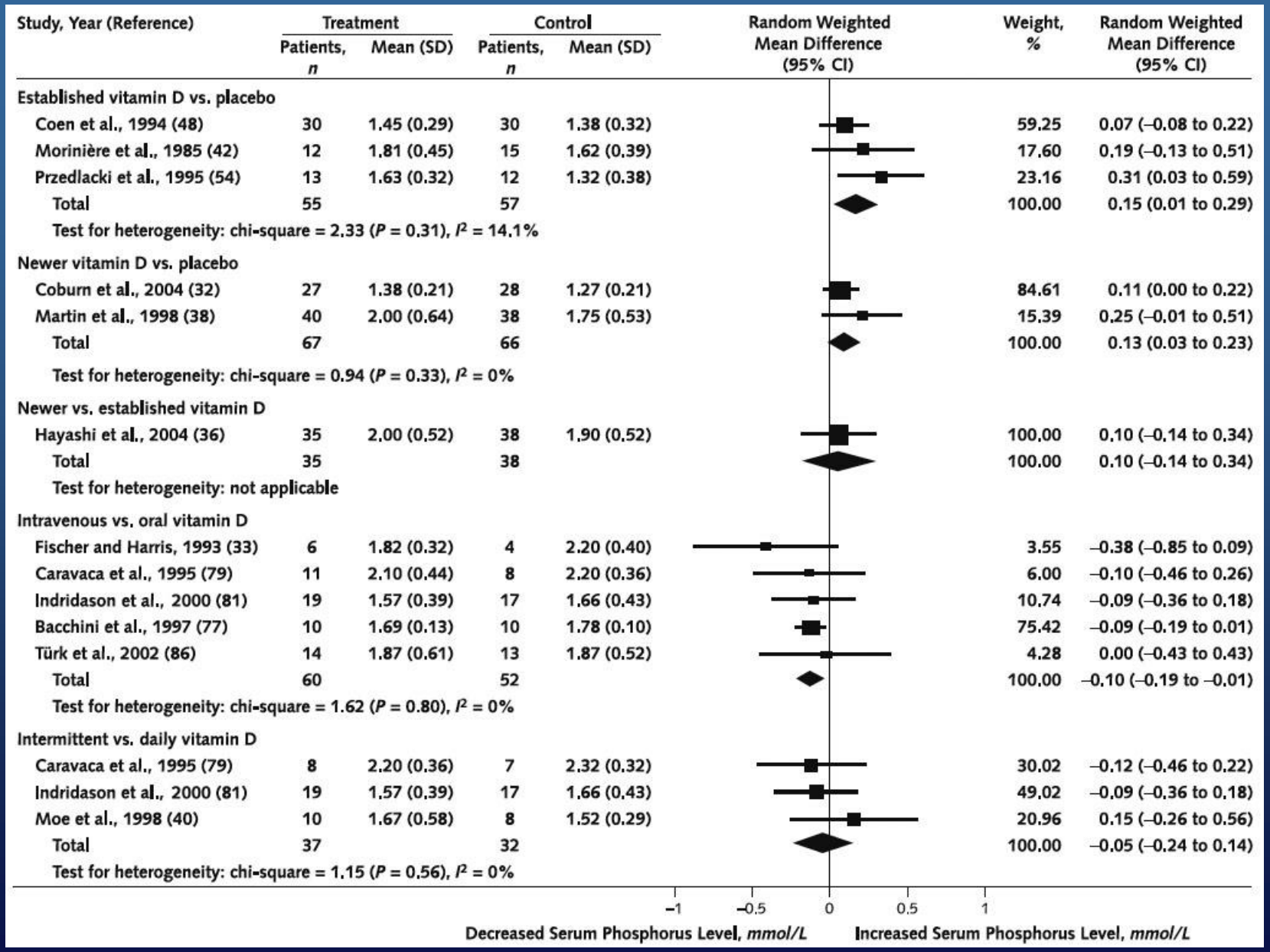


Behets G, PhD thesis, 2005

Circulating 25(OH)D as a Function of Oral Vitamin D_3 Intake



Effect of VitD vs placebo or other interventions on serum P in CKD



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

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