Optimal use of Vit. D in CKD

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Introduction

- The value of using vitamin D to treat 'renal bone disease' is now **nearly six decades** old.
- However, it is more like **three decades, at most**, that we have routinely been using vitamin D to try to prevent, or reverse, the impact of hyperparathyroidism on the skeleton of CKD patients.

Box 1: **Milestones in vitamin D knowledge**

- Chu HI and Liu SH: discovery of vitamin D resistance, 1940.
- Holick MF and De Luca HF: discovery of $1,25(OH)_2$ vitamin D, the most potent vitamin D, 1970.
- Fraser DR and Kodicek E: central role of the kidney for the synthesis of $1,25(OH)_2$ vitamin D, 1970.
- Brickman AS, Coburn JW and Massry SG: first study testing $1,25(OH)_2$ vitamin D in a uremic man, 1974.
- Llach F and Massry SG: accurate documentation of the role of phosphate in the control of $1,25(OH)_2$ vitamin D levels in early renal failure, 1985.
- Shimada T: fibroblast growth factor 23 reduces the renal expression of 25(OH)D 1α–hydroxylase, 2004.
- Holick MF: *New England Journal of Medicine* review focusing on the pervasive nature of vitamin D deficiency and insufficiency at population levels and in disparate disease states, 2007 (8407 quotations as of 21 March 2016).

David J.A. Goldsmith, NDT. (2016)31 (5): 698-705.

Introduction

- The common practice has been to use high and fixed doses of synthetic vitamin D, not naturally occurring ones.

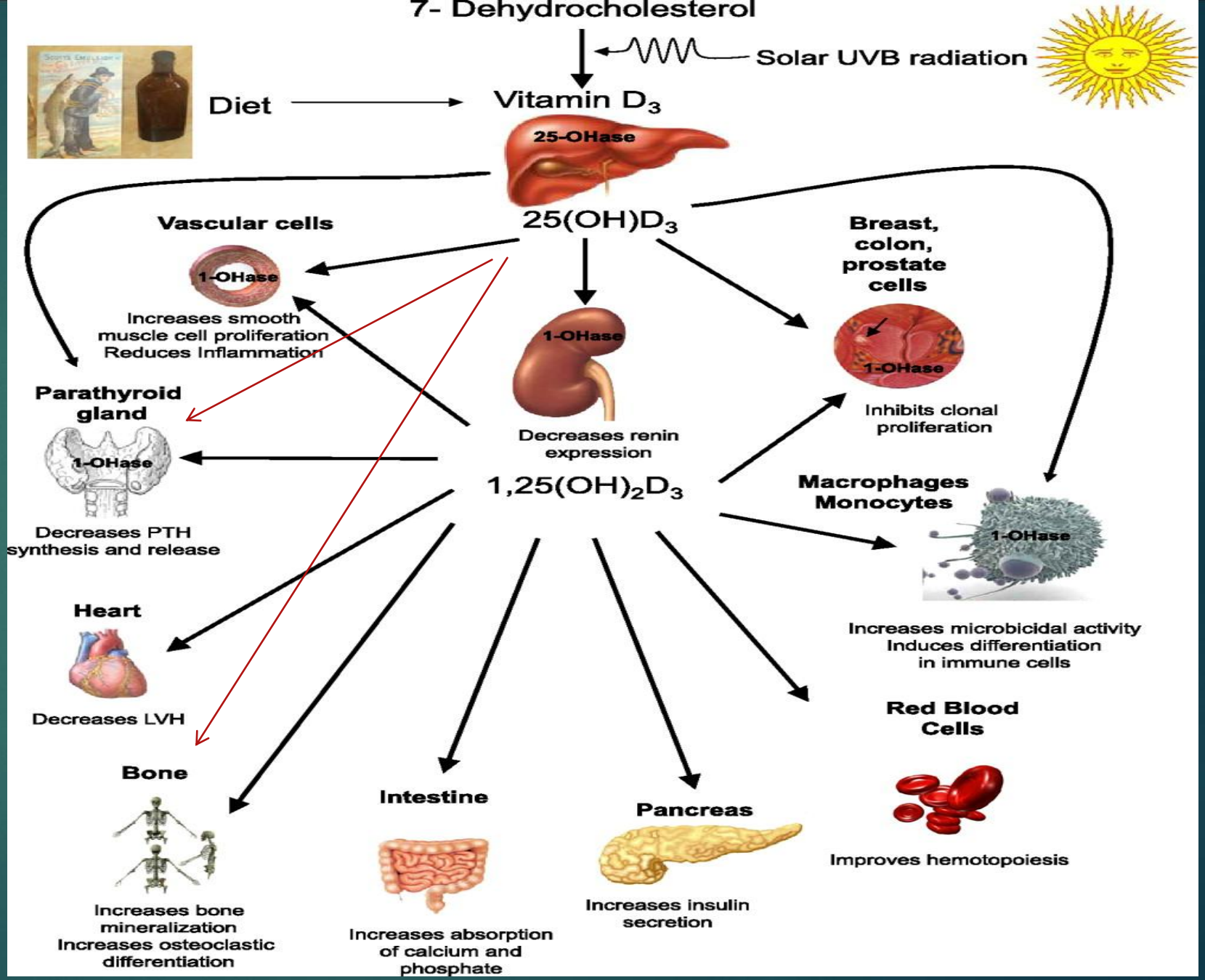
David J.A. Goldsmith, NDT. (2016)31 (5): 698-705.

Agenda

- Functions of different types of Vit.D
- Vit D Status in healthy and CKD patients
- Which Vit D to Use
- Evidence of benefits
- Vit. D Ds:
  - Dilemma, Disappointments

Why would we need vit D?

Physiological functions of Vit. D



José M. Valdivielso, et al,. American Journal of Physiology 2009

Why would we need vit D supplement?

- 1- to replenish vit D
- 2- to increase Ca levels
- 3- to control PTH
- 4- Skeletal effects
- 5- other
  - CVD, Mortality, Immunity

Uses of vit D

- 1- to replenish vit D

Vit D deficiency (Normal Population)

Mayo clinic PMID*: 20675513		Institute of Medicine (IOM) PMID*: 21118827		Pilz et al. PMID*: 21682758		Kidney Disease Improving Global Outcomes (KDIGO) PMID*: 19644521	
Severe deficiency	<25	At risk of deficiency	<30	Deficiency	<50	Deficiency	<37
Moderate deficiency	25–59.9	At risk of inadequate level	30–49	Insufficiency	50–74.9	Insufficiency	37–75
Optimal	60–200	Sufficient	50–125	Optimal	75–100	Adequate	>75
Possible toxicity	>200	Possible toxicity	>125	Sufficiency	75–250		
				Intoxication	>375–500		

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Deficiency	<37
Insufficiency	37–75
Adequate	>75

- Pludowski, et al., International Journal of Endocrinology, 2014

Vit. D Status in healthy and CKD patients

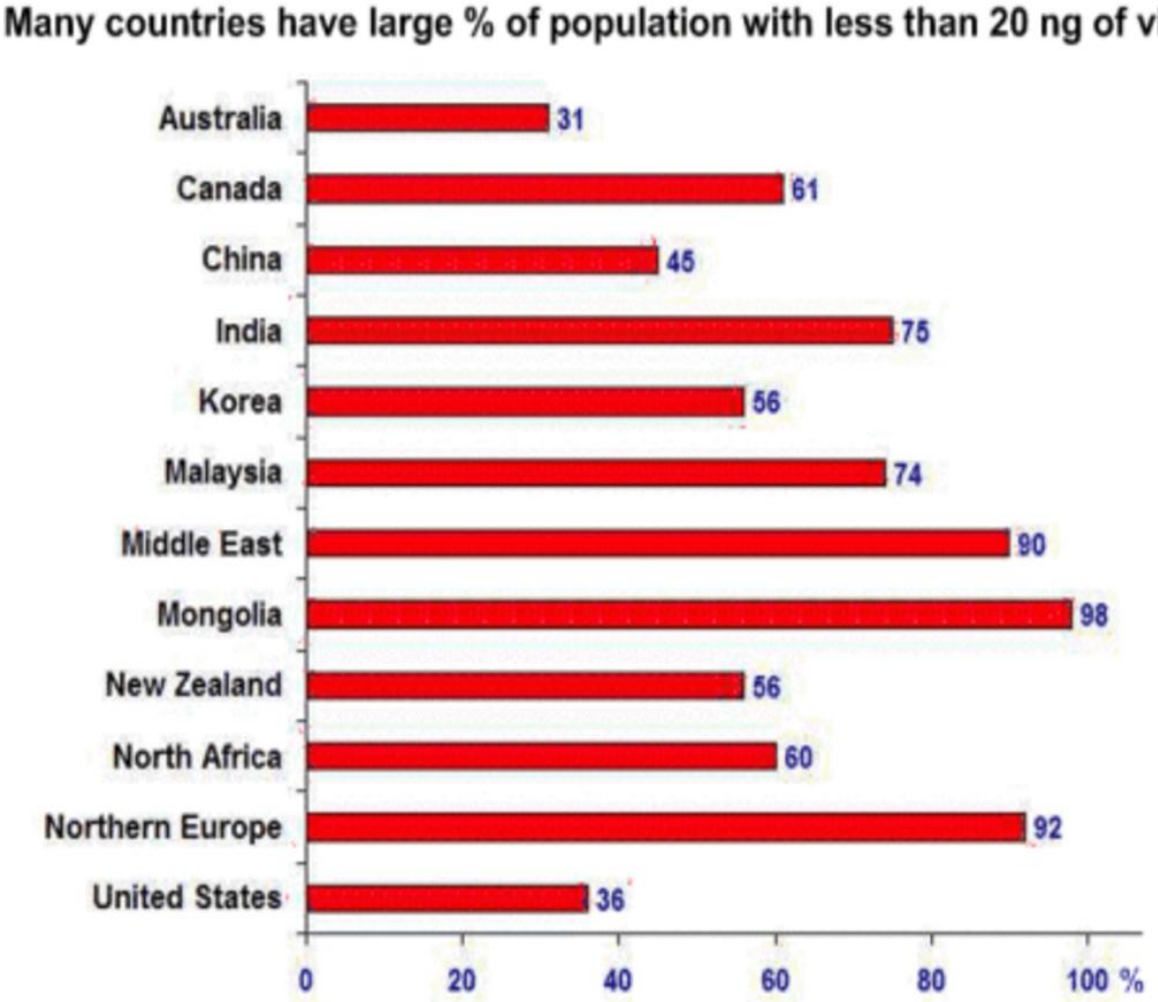
Vit. D Status in healthy population

Table 2. Prevalence of Vitamin D deficiency (<20 ng/mL) and insufficiency (<32 ng/mL) in various athletic populations.

Type of Athlete	Indoor/Outdoor	Gender	Vitamin D Status	Reference
Finnish military recruits	Combination	Male	39% deficient	Valimaki *et al.* [8]
UK professional athletes (jockeys, rugby, soccer)	Combination	Male	62% deficient	Close *et al.* [39]
UK athletes (football, rugby)	Combination	Male	57% deficient	Close *et al.* [40]
Middle Eastern sportsman	Combination	Male	32% insufficient 58% deficient	Hamilton *et al.* [33]
Australian gymnasts	Indoor	Female	33% insufficient	Lovell [36]
Israeli athletes & dancers	Indoor	Male & Female	73% insufficient	Constantini *et al.* [35]
USA indoor/outdoor athletes	Combination	Male & Female	12% insufficient	Halliday *et al.* [37]
USA endurance athletes (runners)	Outdoor	Male & Female	42% insufficient 11% deficient	Willis *et al.* [2]
USA outdoor athletes (rugby, football, track, cross country)	Outdoor	Male	25% insufficient	Storlie *et al.* [38]

Dana Ogan, and Kelly Pritchett, Nutrients 2013

Percent of population with less than 20 ng of vitamin D has the following graph



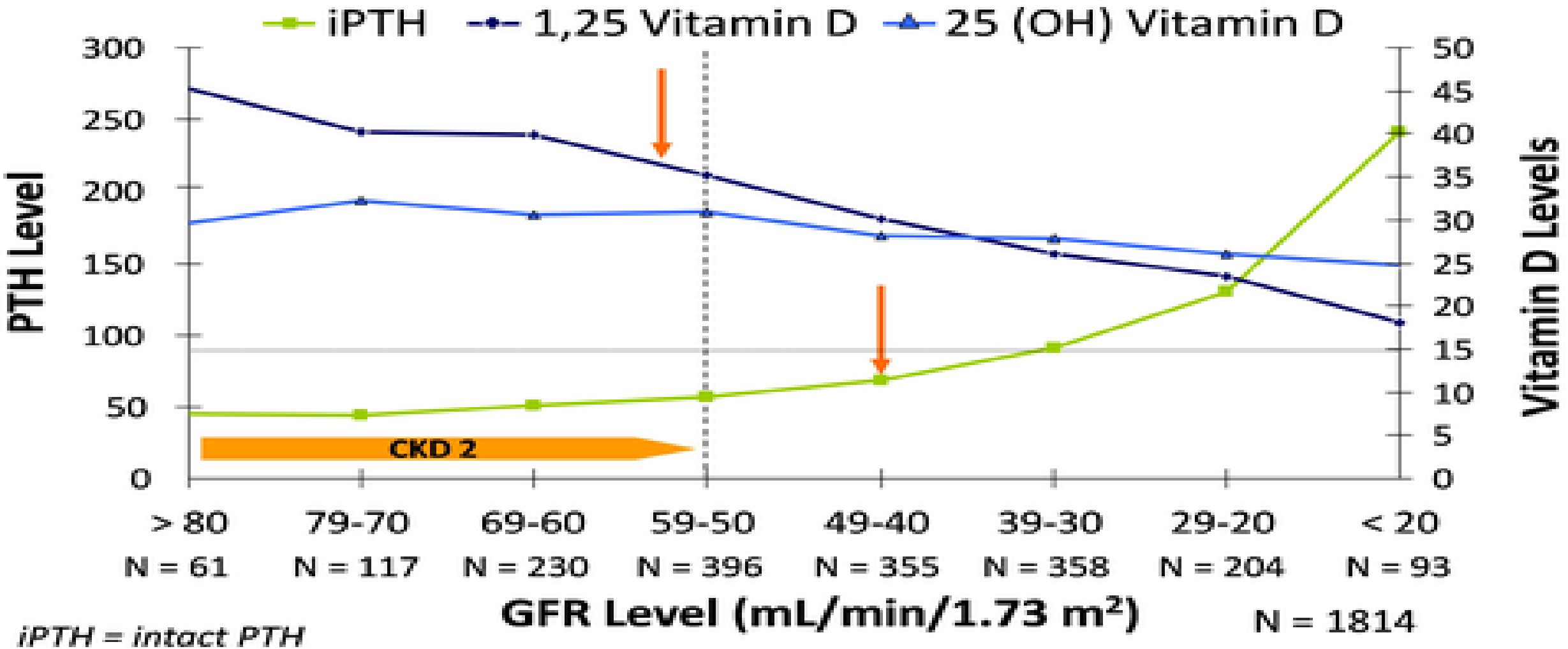
Michael F. Holick, The Journal of Clinical Endocrinology & Metabolism March 22, 2012

Large % of people in many countries have less than 20 nanograms:

Australia 31, Canada 61, China 45, India 75, Korea 56, Malaysia 74, Middle East 90, Mongolia 98, New Zealand 56, North Africa 60, Northern Europe 92, United States 36

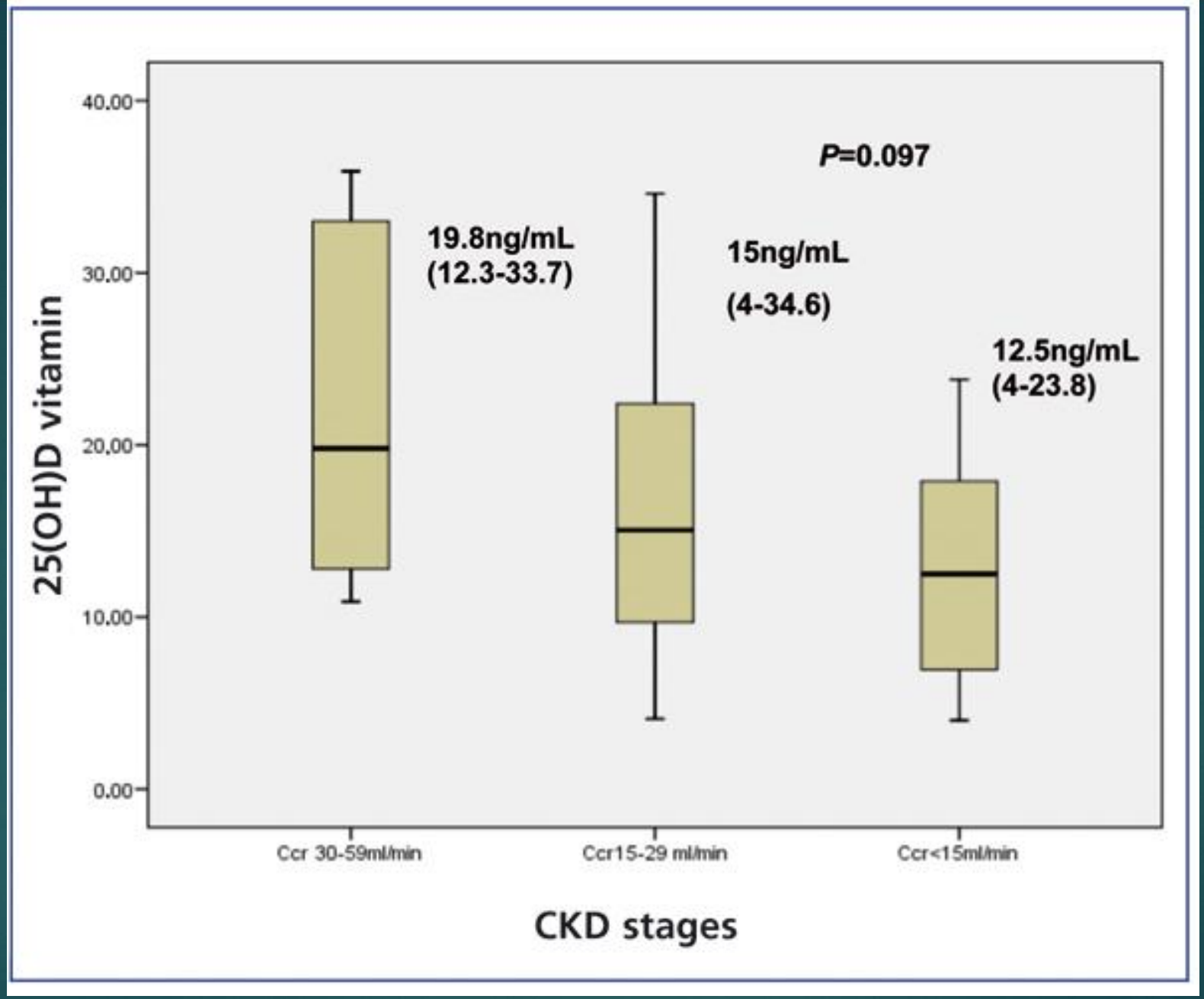
Vit. D Status in CKD patients

Progression of iPTH, Corrected Calcium, and Phosphorus Levels



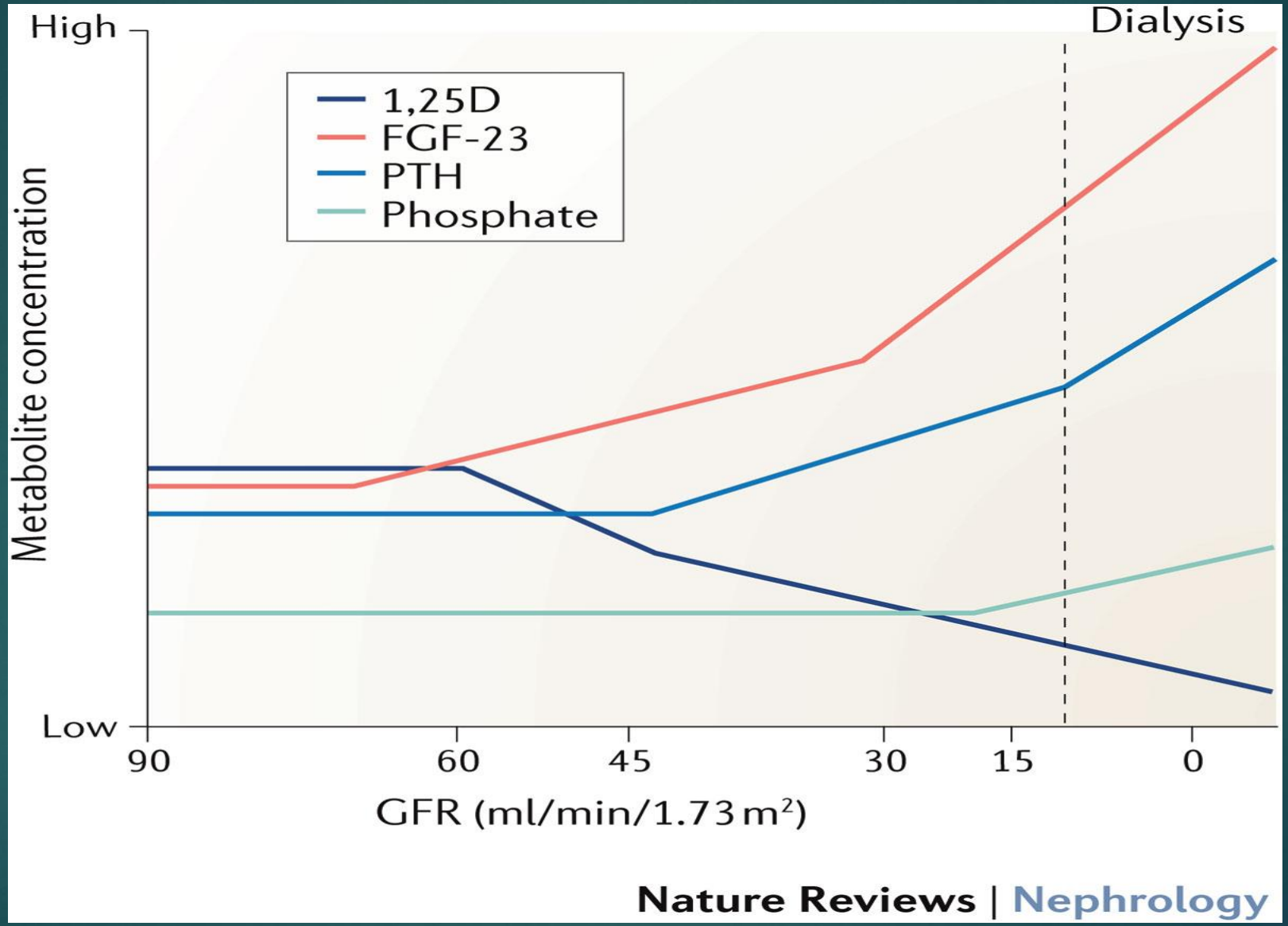
iPTH = intact PTH

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



VILLARREA_Nefrologia (English Version).2011

Figure 4 Model of changes in the serum levels of fibroblast growth factor 23 (FGF-23), 1,25 dihydroxyvitamin D (1,25D), parathyroid hormone (PTH) and phosphate during progression of chronic kidney disease

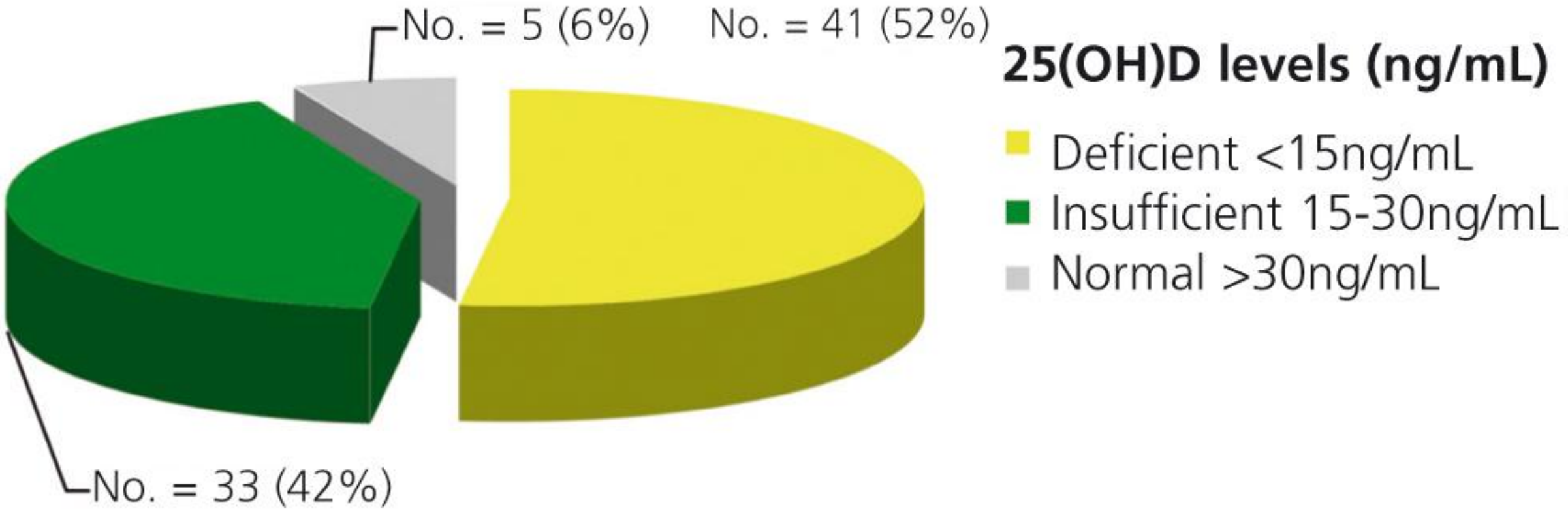


Vervloet, M. G. *et al.* (2016) The role of phosphate in kidney disease
Nat. Rev. Nephrol. doi:10.1038/nrneph.2016.164

Vit. D deficiency in CKD patients

- Studies have reported varying prevalence rates of vitamin D deficiency in CKD **as high as 70% to 80%** prevalence in some parts of the world.

Ginde et al, Arch Intern Med 2009



ISABEL RODRÍGUEZ Nefrologia (English Version) 2011

Why would we need vit D

- **1- to replenish vit D** **YES**
- 2- to increase Ca levels
- 3- to control PTH
- 4- Skeletal effects
- 5- other
  - CVD, Mortality, and morbidly

Why would we need vit D

- 1- to replenish vit D
- 2- to increase Ca levels
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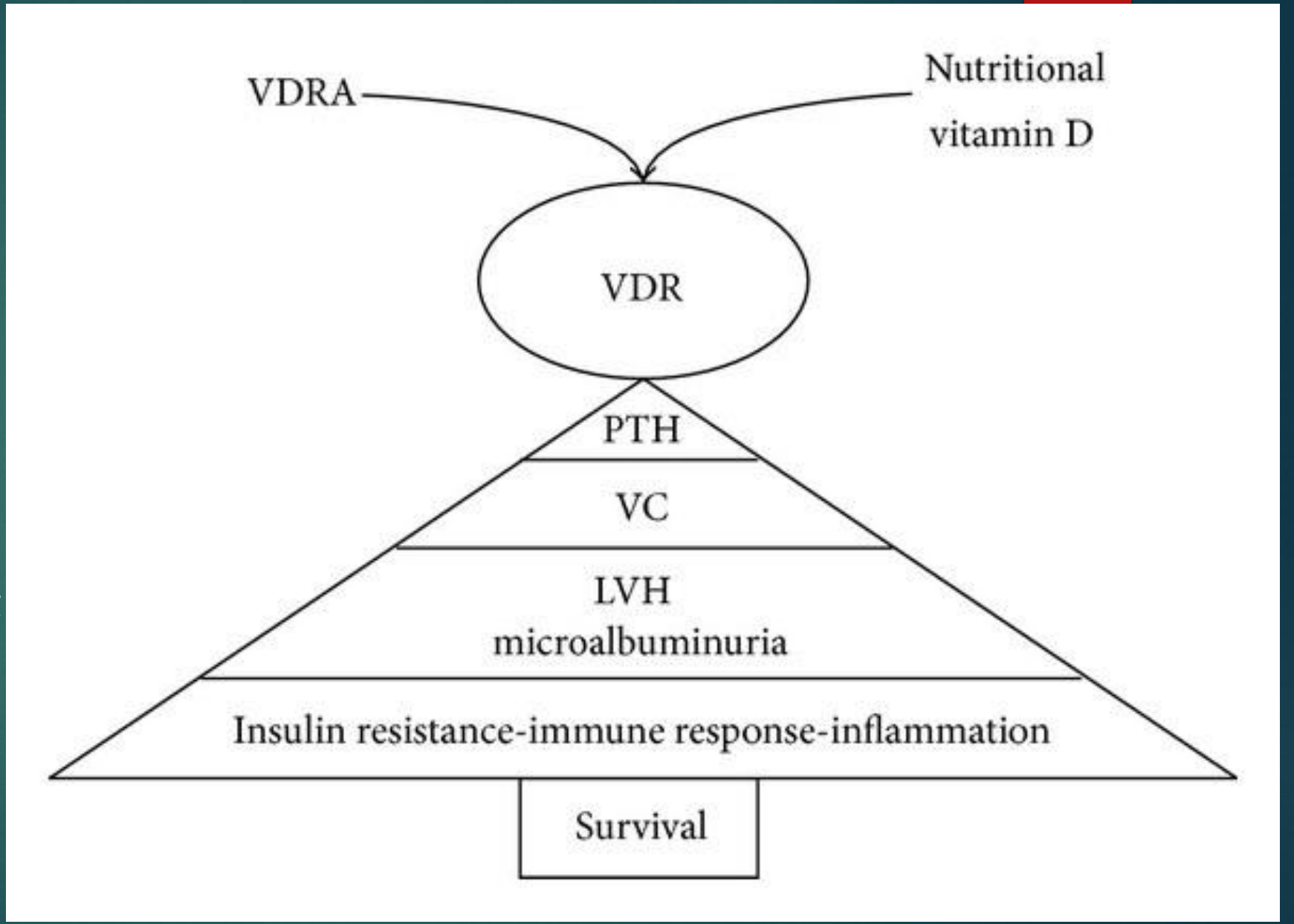
The growing targets of active and native vitamin D.
LVH:
VC: vascular calcification;
VDR: vitamin D receptor;
VDRA: vitamin D receptor activators.



kidney INTERNATIONAL
Official journal of the International Society of Nephrology

Translational Nephrology

Kidney International (2010) **78,** 134–139; doi:10.1038/ki.2009.175; published online 27 May 2009

Renoprotective effects of vitamin D analogs

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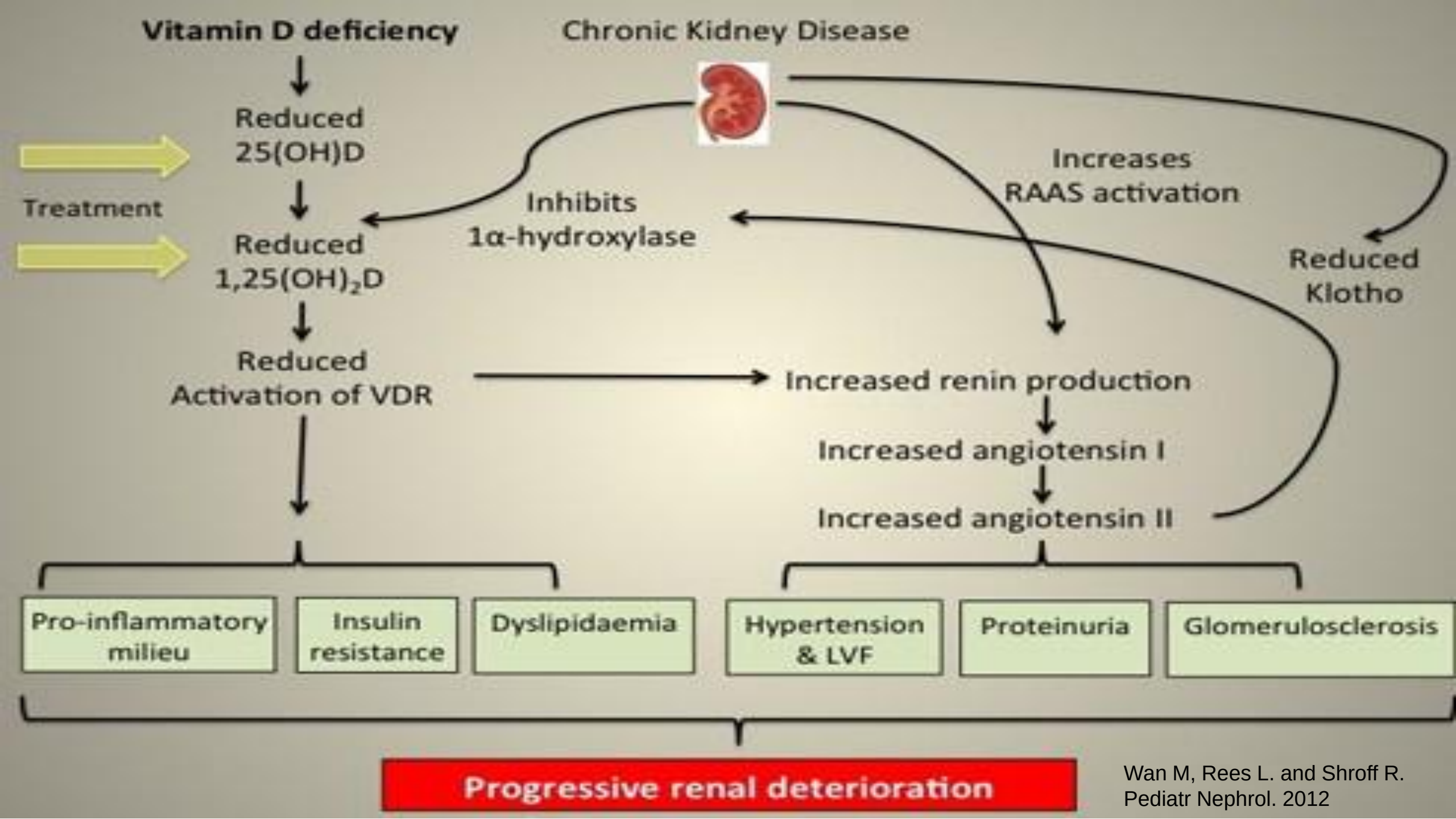
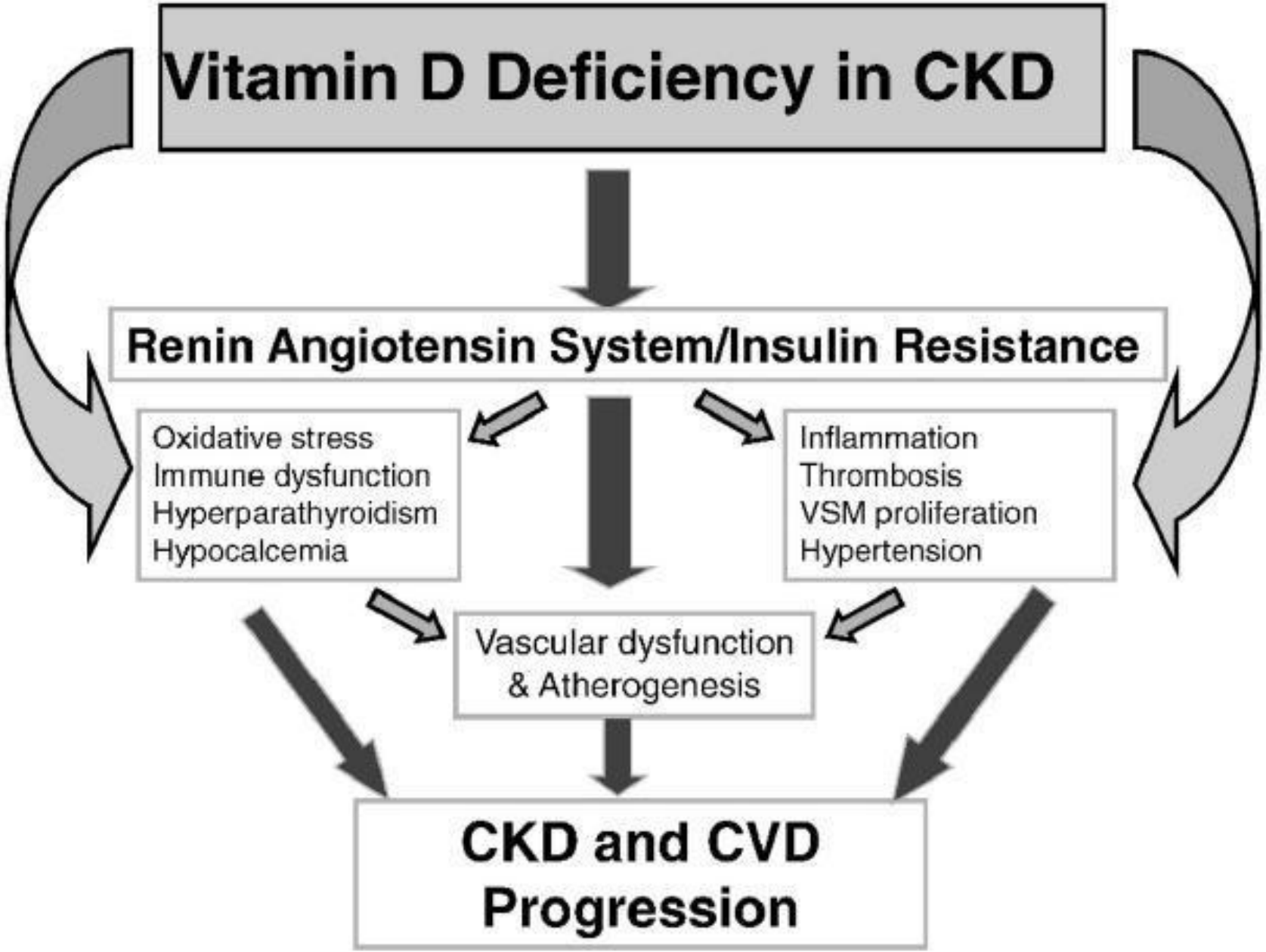
Abstract

Top

Recent decades have witnessed the revelation of expanding roles of the vitamin D endocrine system beyond calcium and phosphorus metabolism. Along with these non-calcemic or non-classic actions of vitamin D are newly discovered therapeutic actions of vitamin D analogs in a number of pathological conditions, including kidney disease. The kidney is the major organ involved in the synthesis of the hormonal metabolite of vitamin D, and vitamin D deficiency is a common feature of chronic kidney disease even in its early stages. Experimental data suggest that vitamin D deficiency may in turn accelerate the progression of kidney disease. Low-calcemic vitamin D analogs have exhibited impressive therapeutic effects



Wan M, Rees L. and Shroff R. Pediatr Nephrol. 2012



Williams S, Malatesta K, Norris K. Ethn Dis. 2009

Proteinuria

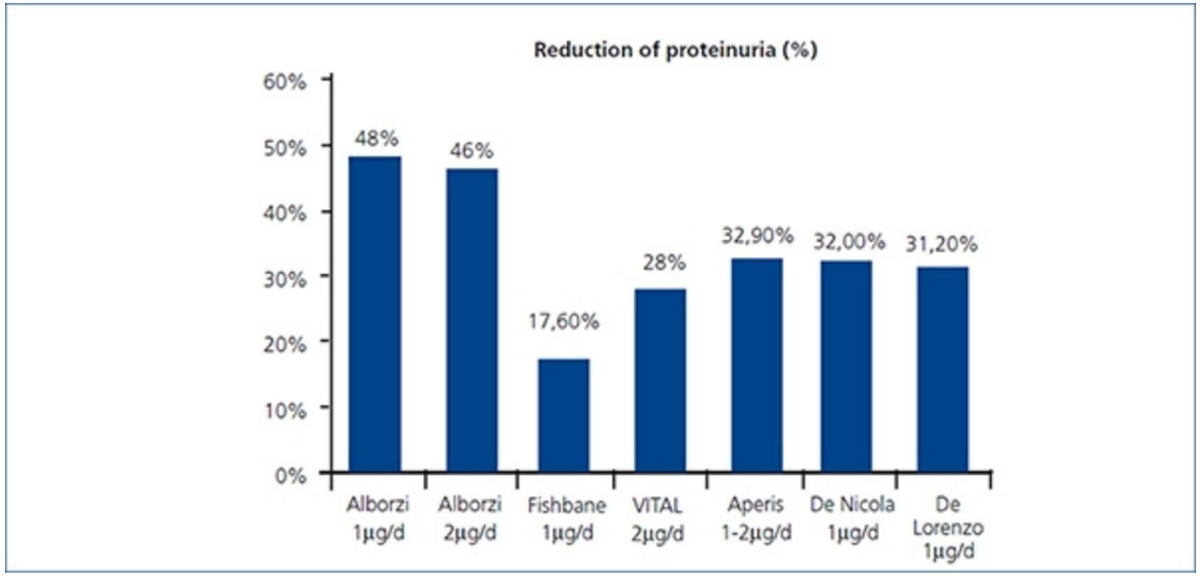


Figure 2. Comparision of proteinuria reduction.
The results of this study are compared alongside those of previous studies of paricalcitol on proteinuria reduction. Percent of reduction in the study performed by Agarwal et al. not published (proteinuria determined by means of a dipstick test).
Proteinuria reduction with 1µg/d in VITAL study resulted no significant.

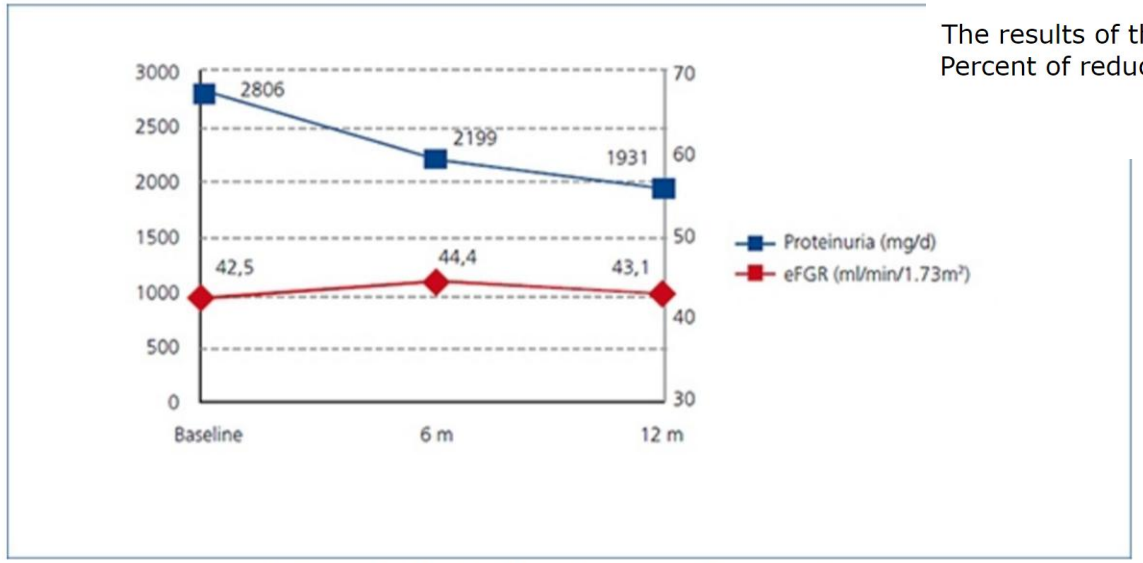
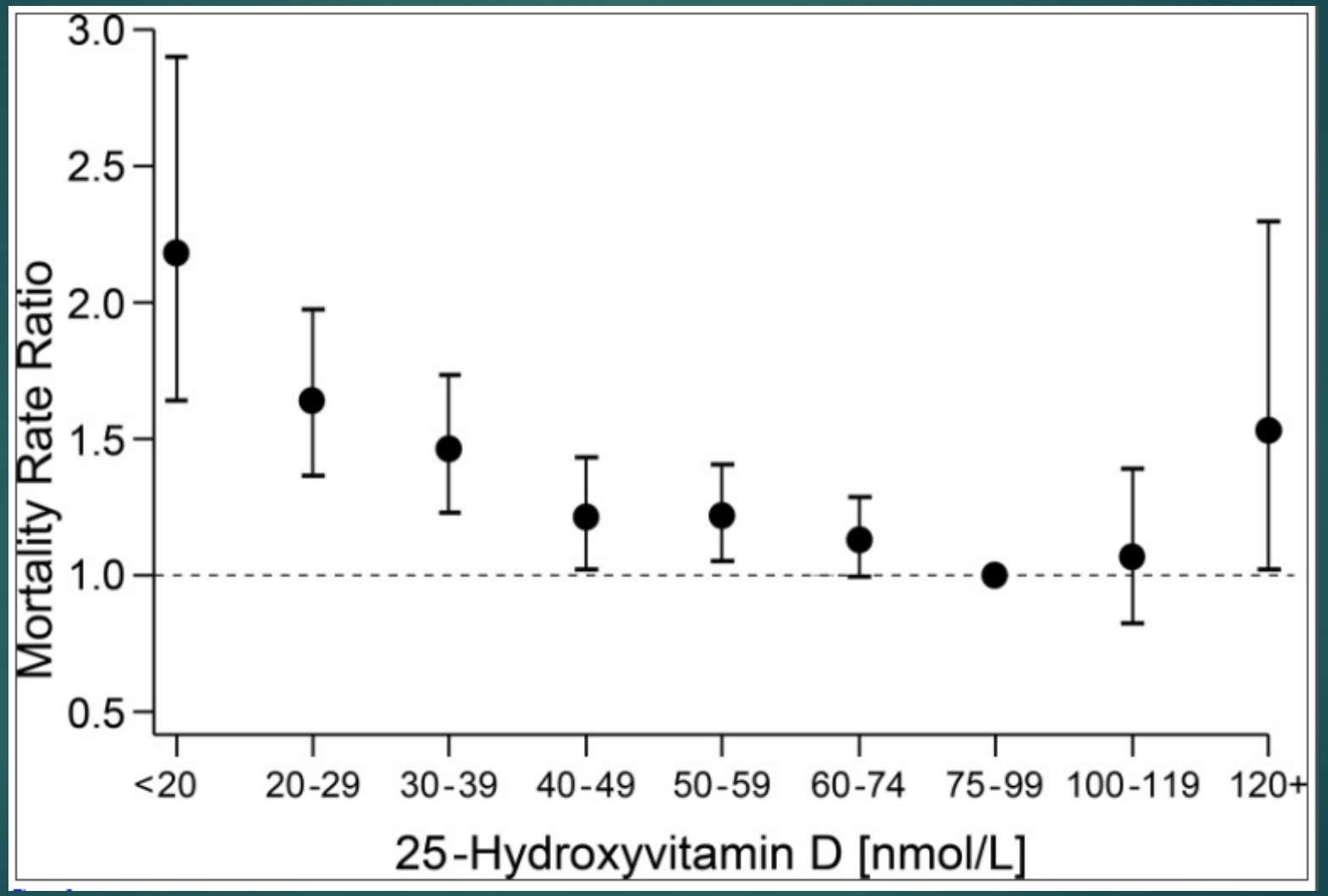


Figure 1. Modification of proteinuria and eGFR.
Mean proteinuria was 2806mg/d and fell to 2199mg/d at month 6 ($p<0.0001$) and 1931.5mg/d at month 12 ($p<0.0001$). There were no significant changes in eGFR between visits.

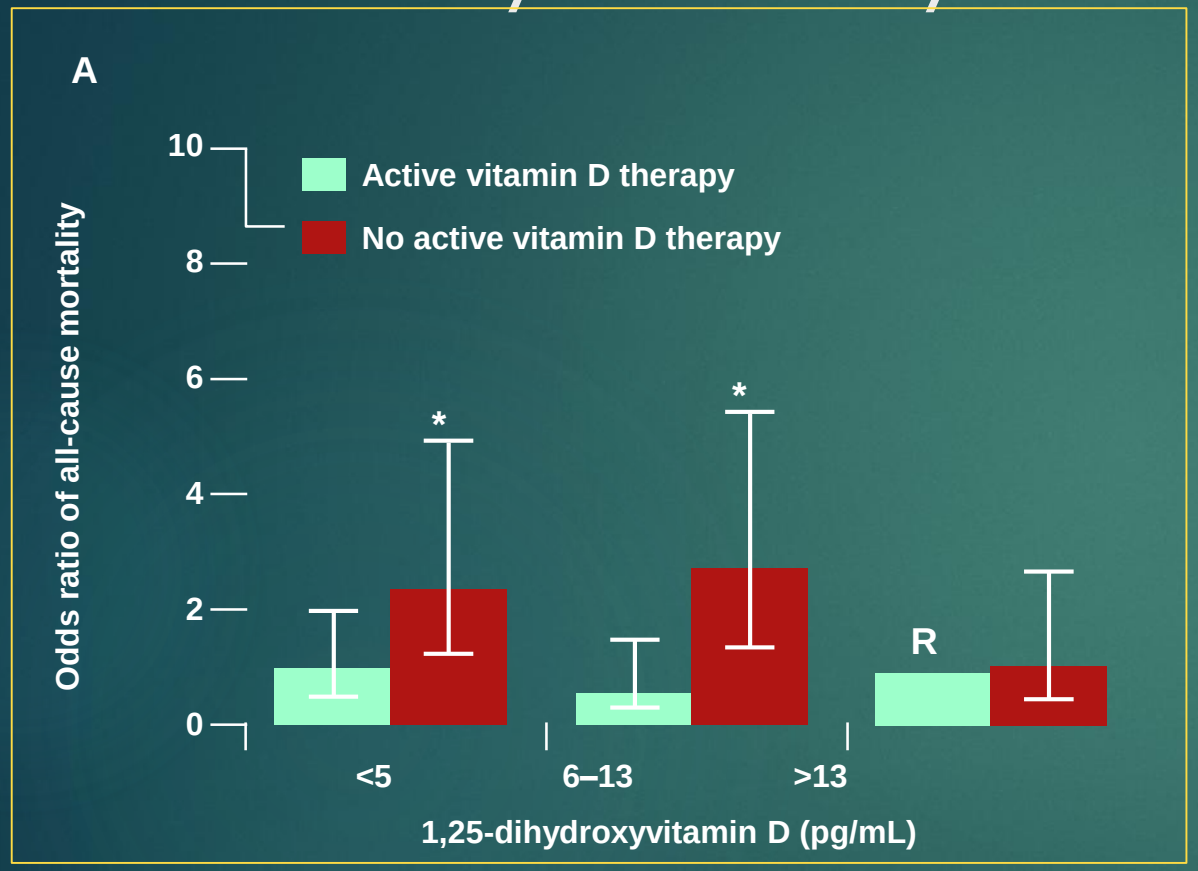
Alberto de Lorenzo et al., Nefrología (Madr.) vol.33 no.5 Cantabria 2013

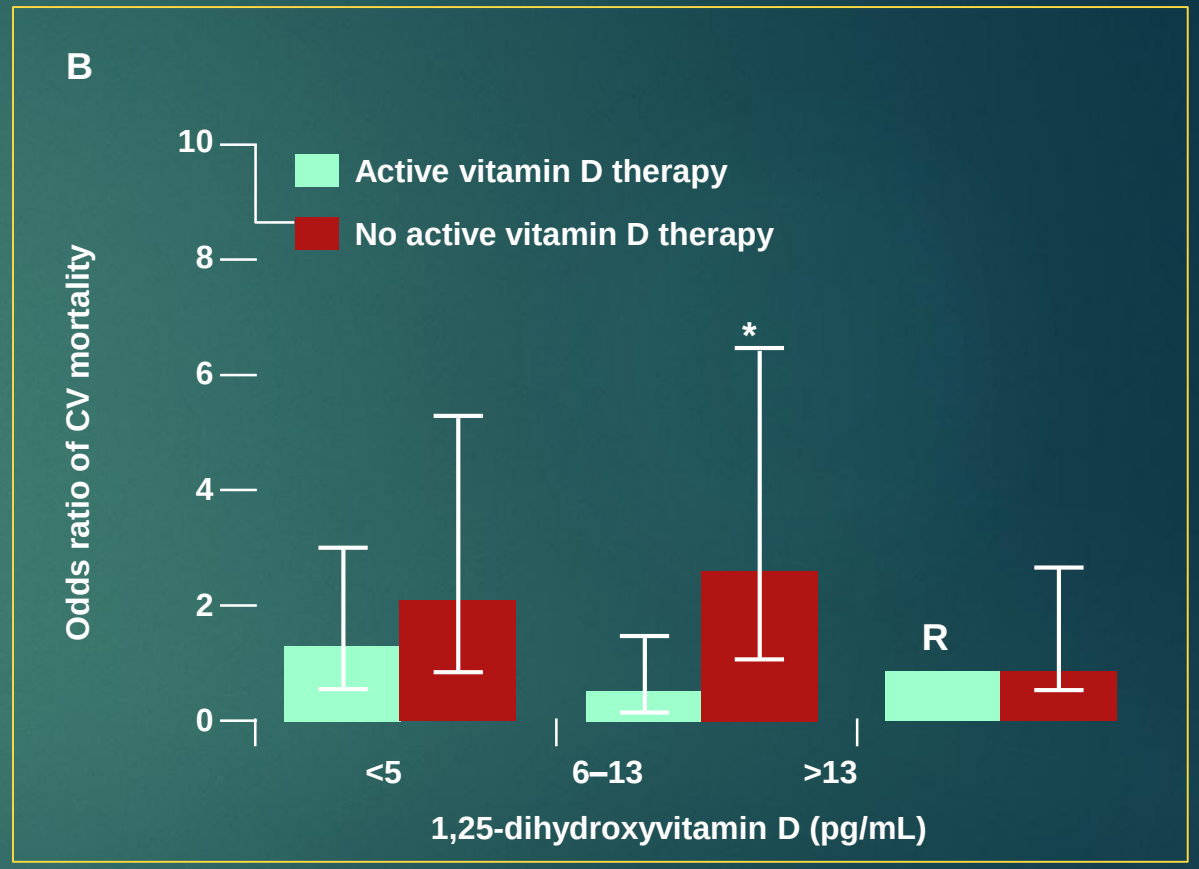
The benefits of Vit D



Chowdhury et al,. BMJ. 2014

$1,25(OH)_2D_3$ Levels and Mortality in Dialysis Patients



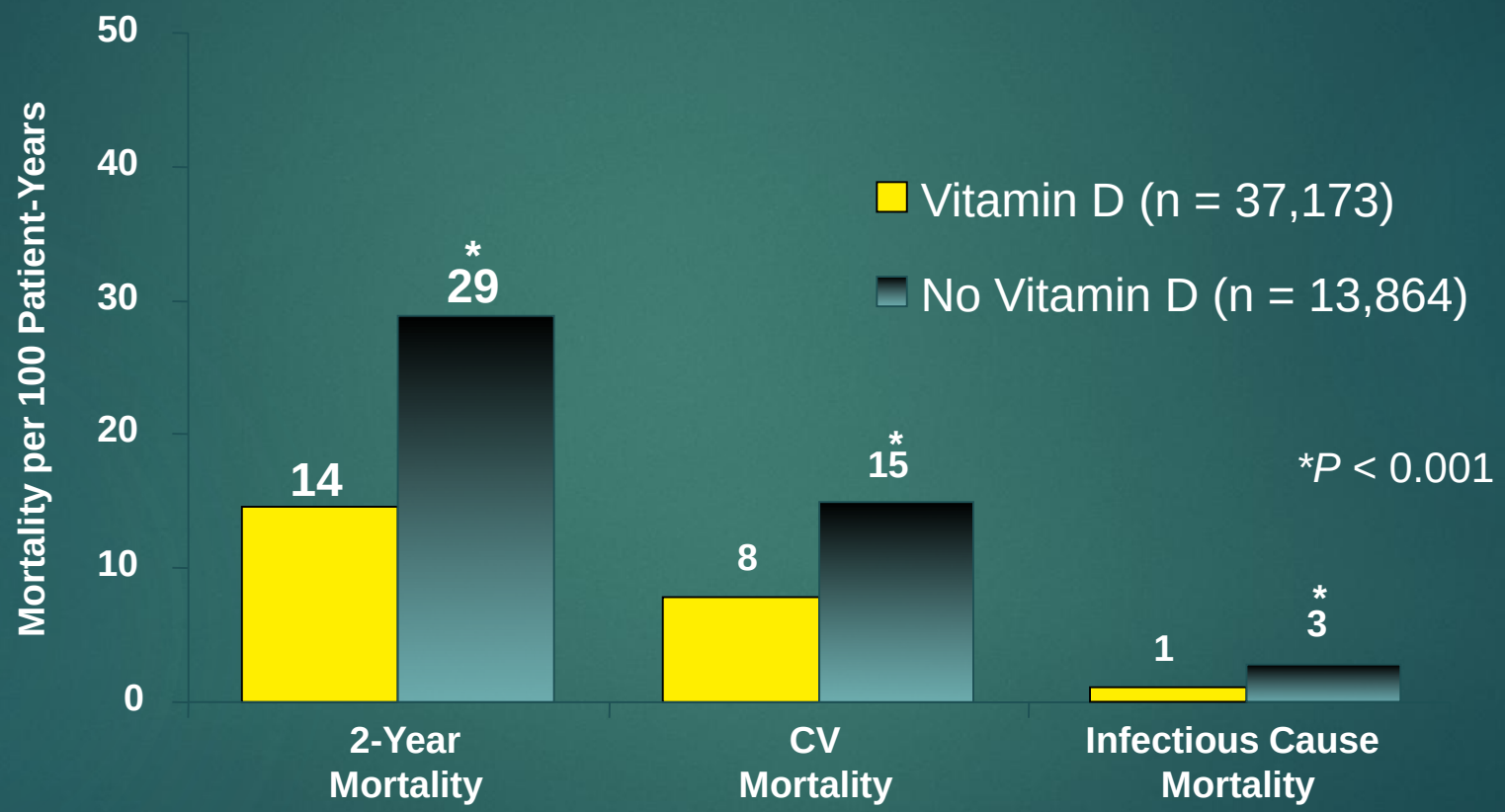


1,25-dihydroxyvitamin D levels and 90-day all-cause (A) and CV mortality (B) in hemodialysis patients according to whether patients received active vitamin D therapy

*P<0.05 for the comparison of the individual vitamin D level—vitamin D treatment groups with the corresponding referent groups.
R=subjects treated with active vitamin D and 1,25-dihydroxyvitamin D levels ≥13 pg/mL.

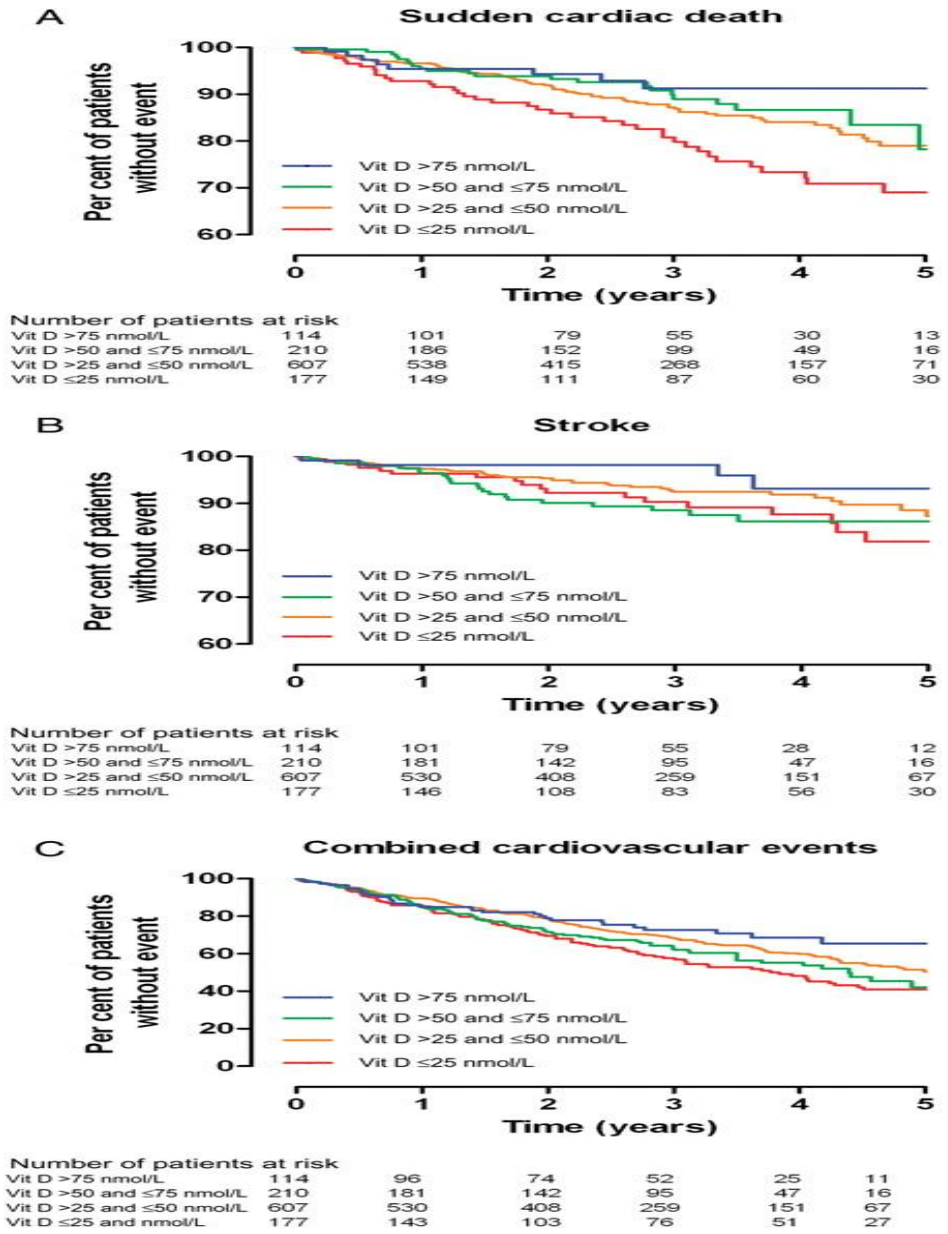
With permission from Wolf M, et al. *Kidney Int*. 2007;72:1004-1013.

Vitamin D Use Is Associated With Decreased Mortality in Incident HD Patients



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

Kaplan–Meier curves for the time to (A) sudden cardiac death, (B) stroke, (C) combined cardiovascular events in subgroups of patients according to 25-hydroxyvitamin D levels at baseline [severely vitamin D deficient (≤25 nmol/L), moderately vitamin D deficient (>25 and ≤50 nmol/L), vitamin D insufficient (>50 and ≤75 nmol/L), and vitamin D sufficient (>75 nmol/L)].



Christiane Drechsler et al. Eur Heart J 2010;31:2253-2261

European Heart Journal

Why would we need vit D

- 1- to replenish vit D
- 2- to increase Ca levels
- 3- to control PTH
- 4- Skeletal effects
- 5-other
  - CVD, Mortality, and morbidity May be

Uses of vit D

- 1- to replenish Vit D
- 2- to increase Ca levels
- 3- to control PTH
- 4- Skeletal effects
- 5- other
  - CVD, Mortality, and morbidity

Vitamin D Treatment in Chronic Kidney Disease

- **Two exclusive vitamin D treatment strategies** for CKD patients are
- **non-activated vitamin D** products (Nutritional), **(cholecalciferol *D3*, ergocalciferol *D2*)** and
- **activated vitamin D** therapy using calcitriol or an analogue.

Al-Aly et al,. Am J Kidney Dis. 2007

Should we use nutritional or should we use active Vit. D to correct Vit.D Deficiency?

- **Would you use:**
  - 1- Natural Vit D. (cholecalciferol *D3*, ergocalciferol *D2*)
  - 2- Active Vit. D
  - 3- Both
  - 4- Either

Nutritional vs active Vit. D

Targets of the use Nutritional vs active Vit. D

- **The use of natural vit D2,& D3 will result in**:
  - 1- Raising serum levels of 25(OH)Vit. D
  - 2- Raising serum levels of 1,25(OH)Vit. D
  - 3- Suppression of PTH
  - 4- Raise s.Ca

American Journal of Kidney Diseases

Volume 50, Issue 1, July 2007, Pages 59–68

Original Investigation

Changes in Serum 25-Hydroxyvitamin D and Plasma Intact PTH Levels Following Treatment With Ergocalciferol in Patients With CKD

Ziyad Al-Aly, MD[1, 2], Rizwan A. Qazi, MD[2], Esther A. González, MD[2], Angelique Zeringue, MS[3], Kevin J. Martin, MBBCh[2]

Show more

Correction of Insufficient 25-hydroxy Vitamin D Levels

- In 66 stage III-IV CKD patients with 25-hydroxy vitamin D levels < 30 ng/mL and hyperparathyroidism,
  - **50,000 units of ergocalciferol weekly** increased mean 25-hydroxy vitamin D levels by 10.6 ng/mL,
  - **decreased PTH** levels by 38 pg/mL, and
  - **did not alter serum calcium or phosphate levels during 6 months of therapy.**
- **Correction** of deficient/insufficient **25-hydroxy vitamin D** levels in CKD results in **a modest reduction in PTH levels, absence of toxicity, and low cost.**

Al-Aly et al,. Am J Kidney Dis. 2007

CJASN Clinical Journal of the American Society of Nephrology

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

Praveen Kandula[*], Mirela Dobre[†‡], Jesse D. Schold[§‖], Martin J. Schreiber Jr[§], Rajnish Mehrotra[¶**], Sankar D. Navaneethan[§]

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Dr. Sankar D. Navaneethan, Department of Nephrology and Hypertension, Cleveland Clinic, 9500 Euclid Avenue, Q7, Cleveland, OH 44195. Phone: 216-636-9230; Fax: 216-444-9378; E-mail: navanes@ccf.org

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This Article

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CJASN **January 2011** vol. 6 no. 1 **50–62**

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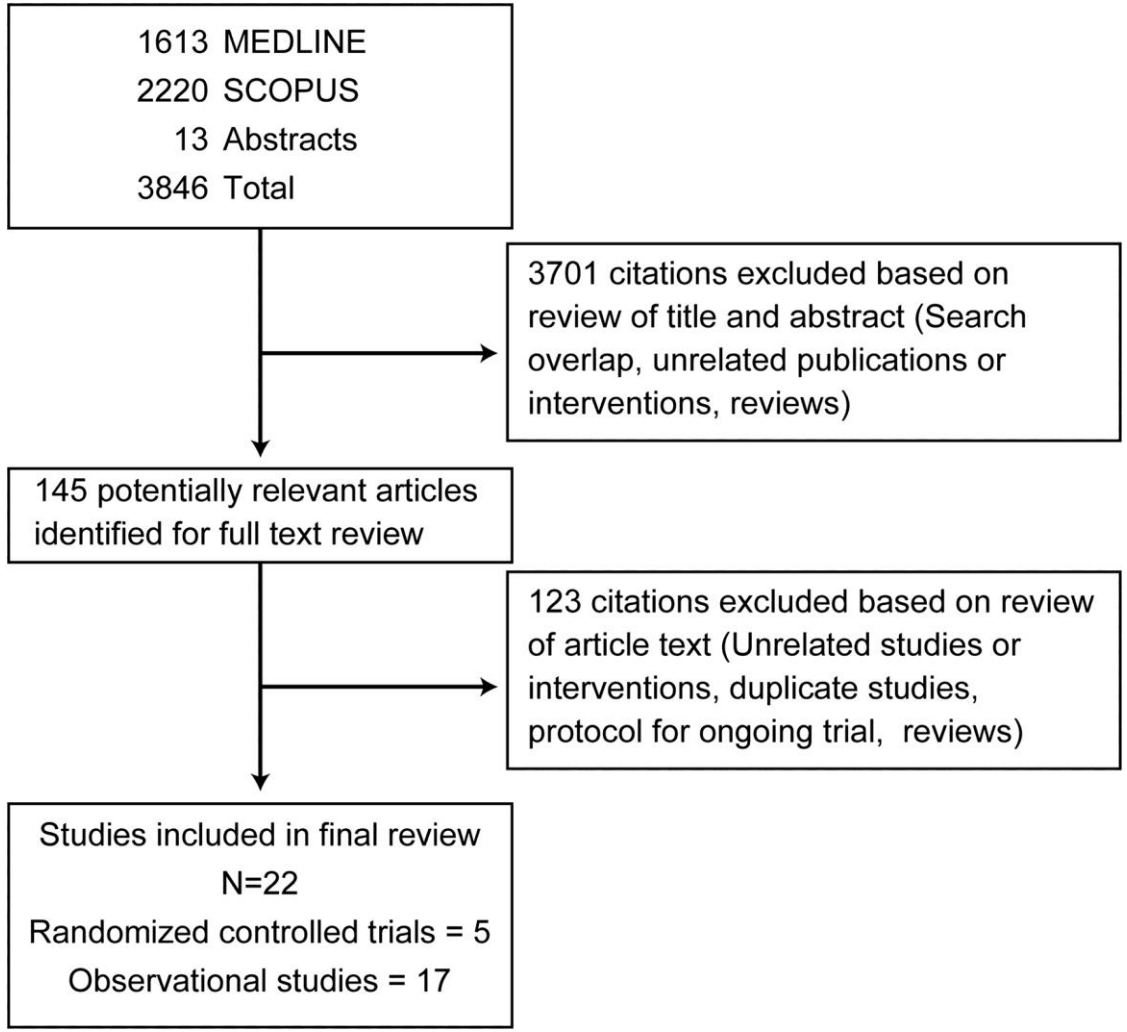
Study flow diagram: Included studies and reasons for exclusion of studies.

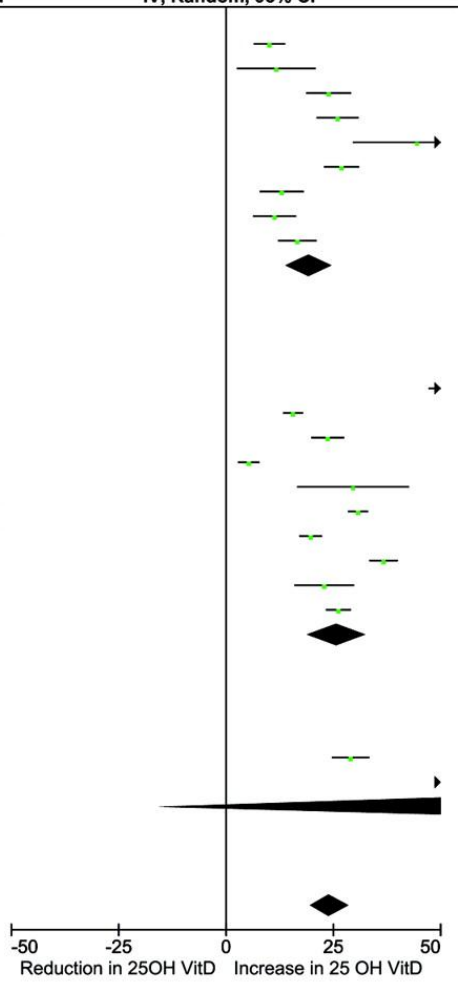


Praveen Kandula et al. CJASN 2011;6:50-62

CJASN

Effect of vitamin D supplementation on 25(OH)D levels at the end of treatment period among *observational studies* in CKD.

Study or Subgroup	Post supplementation Mean	SD	Total	Baseline Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Predialysis								
Al Aly 2007 Stage 3	27.6	11.27	44	17.5	5.3	44	5.3%	10.10 [6.42, 13.78]
Al-Aly 2007 Stage 4	26.4	21.1	22	14.7	6.09	22	4.5%	11.70 [2.52, 20.88]
Deville 2006 Stage 3	41.5	11	26	17.6	8	26	5.1%	23.90 [18.67, 29.13]
Deville 2006 Stage 4	44.7	16	51	18.7	8	51	5.2%	26.00 [21.09, 30.91]
Finn 2007	60.2	33.9	20	15.7	3.9	20	3.4%	44.50 [29.54, 59.46]
Lopes 2009	38.2	11.7	33	11.3	2.7	33	5.3%	26.90 [22.80, 31.00]
Shannon 2007	34.43	11.57	38	21.46	11.2	38	5.1%	12.97 [7.85, 18.09]
Zisman 2007 CKD 3	31.6	10.77	24	20.3	6.36	24	5.2%	11.30 [6.30, 16.30]
Zisman 2007 CKD 4	35.4	10.05	28	18.8	6.87	28	5.2%	16.60 [12.09, 21.11]
Subtotal (95% CI)			**286**			**286**	**44.3%**	**19.33 [13.93, 24.74]**
Heterogeneity: Tau² = 57.78; Chi² = 75.76, df = 8 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 7.01 (P < 0.00001)								
1.1.3 Dialysis								
Bagnis 1998	71	33	15	7	4	15	3.1%	64.00 [47.18, 80.82]
Balon 2009	27	8.6	77	11.4	6	77	5.4%	15.60 [13.26, 17.94]
Blair 2008	42.04	24.71	171	18.35	8.99	318	5.3%	23.69 [19.86, 27.52]
Bouchard 2008	17.8	5.4	27	12.5	3.9	27	5.4%	5.30 [2.79, 7.81]
Deville 2006 Stage 5	45.7	17	8	16.1	8	8	3.8%	29.60 [16.58, 42.62]
Jean 2009	44.08	11.25	107	13.33	5.4	107	5.4%	30.75 [28.39, 33.11]
Matias 2009	42	12.1	158	22.3	12	158	5.4%	19.70 [17.04, 22.36]
Saab 2007	53.6	16.3	118	16.9	8.5	118	5.3%	36.70 [33.38, 40.02]
Shah 2005	29.77	17.01	23	6.9	0.22	23	4.9%	22.87 [15.92, 29.82]
Tokmak 2008	33.11	11.3	64	6.93	4	64	5.4%	26.18 [23.24, 29.12]
Subtotal (95% CI)			**768**			**915**	**49.4%**	**25.87 [19.00, 32.75]**
Heterogeneity: Tau² = 111.63; Chi² = 362.45, df = 9 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 7.38 (P < 0.00001)								
1.1.4 Transplant								
Courbebaisse 2009	43	14	47	14	6.25	47	5.2%	29.00 [24.62, 33.38]
Pessenson 2007	134.7	76	14	17.7	8	14	1.0%	117.00 [76.97, 157.03]
Subtotal (95% CI)			**61**			**61**	**6.3%**	**70.66 [-15.46, 156.77]**
Heterogeneity: Tau² = 3660.93; Chi² = 18.34, df = 1 (P < 0.0001); I² = 95%								
Test for overall effect: Z = 1.61 (P = 0.11)								
Total (95% CI)			**1115**			**1262**	**100.0%**	**24.13 [19.62, 28.64]**
Heterogeneity: Tau² = 96.39; Chi² = 486.31, df = 20 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 10.48 (P < 0.00001)								
Test for subgroup differences: Chi² = 29.75, df = 2 (P < 0.00001), I² = 93.3%								



Praveen Kandula et al. CJASN 2011;6:50-62

CJASN

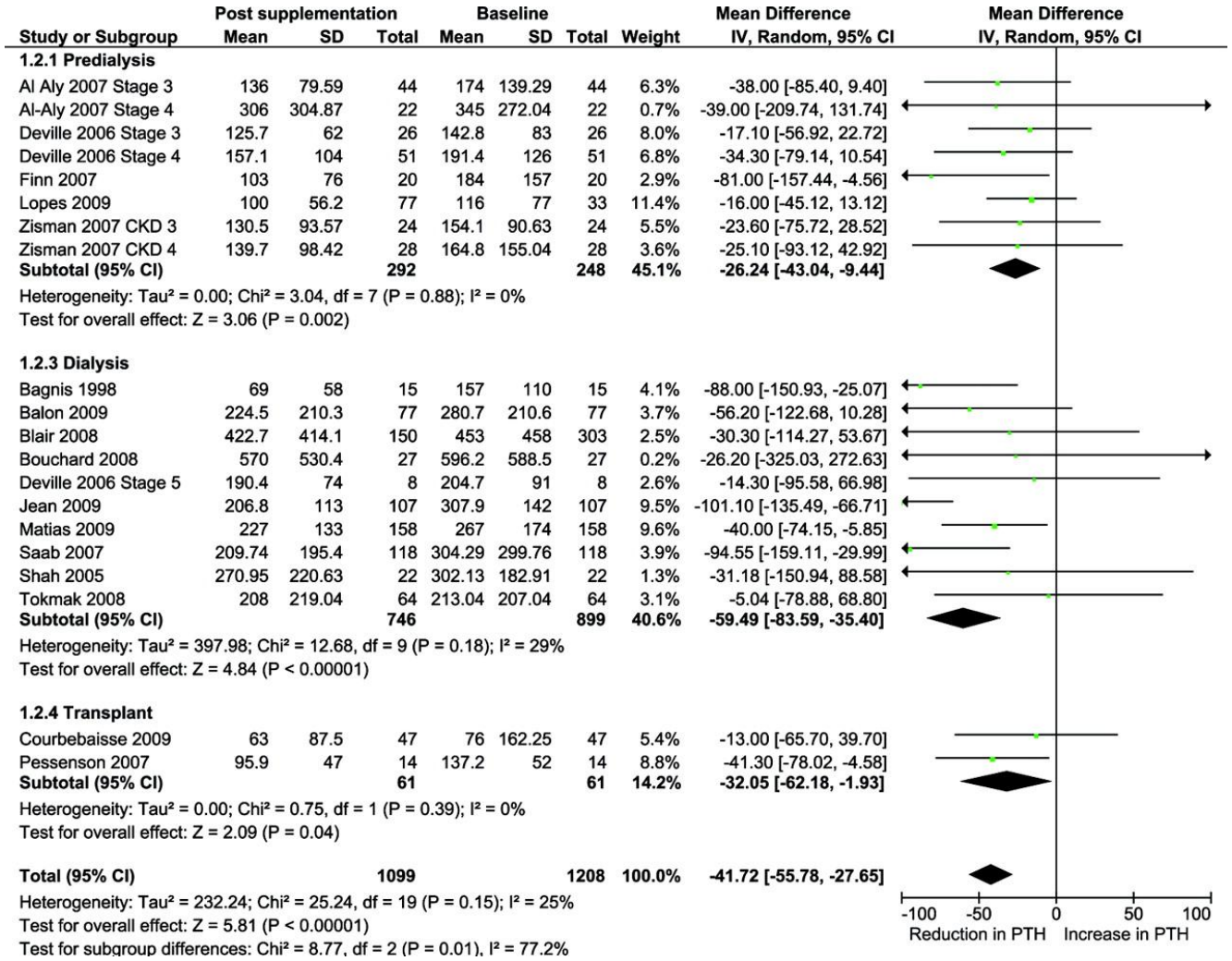
1,25(OH)2D Levels:

- **Observational Studies.**
- Overall **there was a significant improvement in the levels of 1,25(OH)2D** with vitamin D supplementation (nine studies, 449 patientsP < 0.00001) with significant heterogeneity between the studies ($\chi 2 = 121.64$, $P < 0.001$; $I2 = 93\%$).

- **RCTs.**
- Although three of the five RCTs reported 1,25(OH)2D levels**, data were not available for calculation** from one study, and another study (compared 5000 IU with 20,000 IU precluding pooling of the data. Both of these studies reported a nonsignificant increase in 1,25(OH)2D levels

Praveen Kandula et al,. CJASN 2011

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



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, 66.98]
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 = 397.98; 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%**	**-32.05 [-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%								

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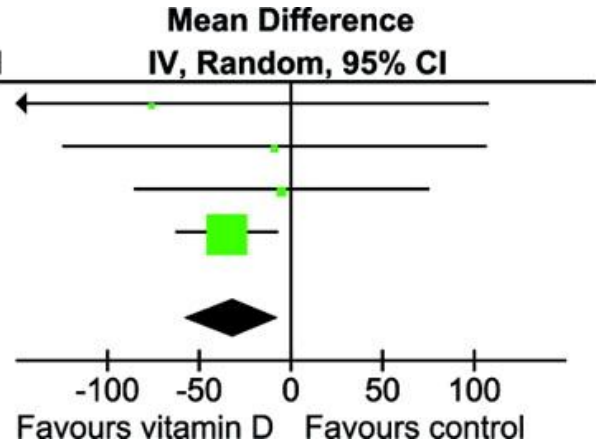
CJASN

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

Study or Subgroup	Vitamin D Mean	SD	Total	Control Mean	SD	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: $Tau^2 = 0.00$; $Chi^2 = 0.84$, df = 3 (P = 0.84); $I^2 = 0\%$

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



Praveen Kandula et al. CJASN 2011;6:50-62

CJASN

Calcium Levels:

- **Observational Studies.**
- There was **no significant change** in serum calcium levels after vitamin D supplementation (16 studies, 1071 patients, MD 0.07 mg/dl, 95% CI −0.03 to 0.17, P = 0.19).

- **RCTs.**
- There was **no significant change** in serum calcium levels with vitamin D supplementation (three studies, 77 patients, MD 0.23 mg/dl, 95% CI −0.31 to 0.77, P = 0.40).

Praveen Kandula et al,. CJASN 2011

Phosphorus Levels:

- **Observational Studies.**
- There was **no significant change** in serum phosphorus levels with vitamin D supplementation (15 studies, 986 patients, MD 0.05 mg/dl, 95% CI −0.11 to 0.22, P = 0.53).

- **RCTs.**
- There was **no significant difference** in serum phosphorus levels with vitamin D supplementation (three studies, 80 patients, MD 0.15 mg/dl, 95% CI −0.19 to 0.49, P = 0.38). One study compared 5000 IU with 20,000 IU vitamin D supplementation and revealed a similar change in phosphorus levels

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Incidence of Hypercalcemia and Hyperphosphatemia

- **Observational Studies.**
- Of the **17 observational** studies, hypercalcemia and hyperphosphatemia incidence were **reported in nine and six studies, respectively.**

- **RCTs.**
- Of **the five** randomized studies, hypercalcemia and hyperphosphatemia data were **reported in four and two studies, respectively.**

Praveen Kandula et al,. CJASN 2011

In conclusion,

- Natural Vitamin D supplementation appears
  - **to improve 25(OH)D and 1,25(OH)2D levels**
  - **While modestly 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.

Praveen Kandula et al,. CJASN 2011

Con: Nutritional vitamin D replacement in chronic kidney disease and end-stage renal disease

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Table 1.

Randomized studies comparing the effect of inactive vitamin D supplementation versus placebo or no treatment on surrogate risk factors in patients with CKD and ESRD

[29]			with 25(OH)D <16 ng/mL	blind	IU weekly for 1 month and monthly later)		micro- and macrocirculatory function		0.78) and LVMI (P = 0.44)
								Positive	Ergocalciferol improved endothelium-dependent vasodilatation after iontophoresis of acetylcholine (P = 0.03)
Studies in ESRD patients									
Delanaye [20]	2013	43	HD patients with 25(OH)D insufficiency	Double-blind	Cholecalciferol (25 000 IU every 2 weeks)	Placebo	12	Change in vascular calcification score	Null	No difference between groups in change of vascular calcification score over time (Deltas: 2 ± 3 versus 2 ± 2, P = 0.89)
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Bhan [19]	2015	105	HD patients with 25(OH)D <32 ng/mL	Double-blind	Ergocalciferol (50 000 IU weekly or 50 000 IU monthly)	Placebo	3	Change in anemia-related parameters	Null	Frequency of intravenous iron use (monthly 39% versus weekly 39% versus placebo 51%, P = 0.49) and EPO use (monthly 71% versus weekly 69% versus placebo 60%, P = 0.61) was no different between groups
Miskulin [24]	2016	276	HD patients with 25(OH)D <30 ng/mL	Double-blind	Ergocalciferol (50 000 IU weekly)	Placebo	6 months	Change in EPO dose	Null	No significant change in weekly EPO dose over time in both groups (geometric mean rate: 0.99; 95% CI: 0.95–1.03)

HD, hemodialysis; CKD, chronic kidney disease; ESRD, end-stage renal disease; BMD, bone mass density; EPO, epoetin; PWV, pulse wave velocity; LVMI, left ventricular mass index; HRQOL, health-related quality of life; CI, confidence intervals; NS, non-significant.

Con: Nutritional vitamin D replacement in chronic kidney disease and end-stage renal disease

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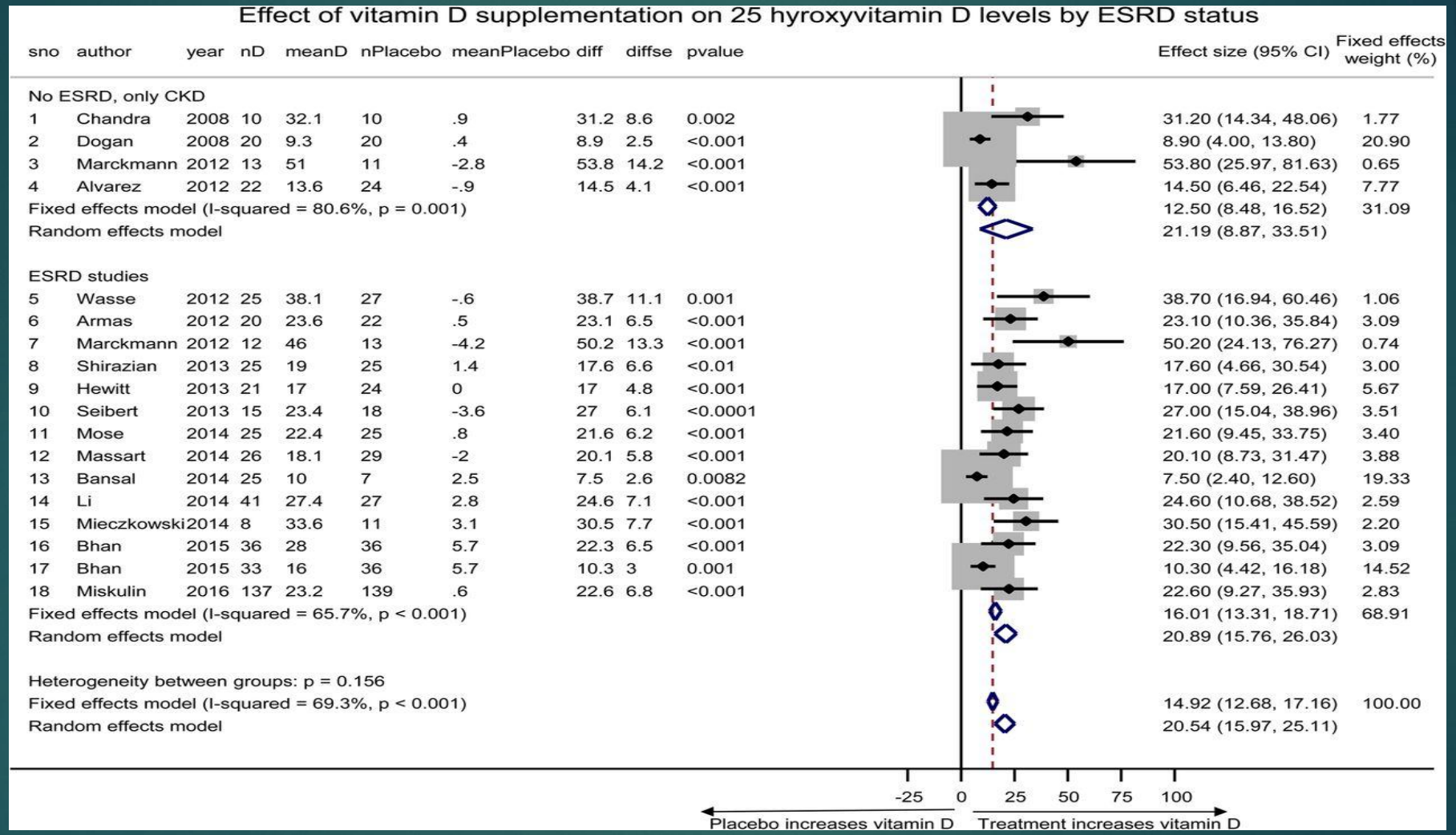
Forest plot depicting the change from baseline in 25(OH)D levels in the ‘nutritional vitamin D group’ minus the change from baseline in the ‘placebo group’.

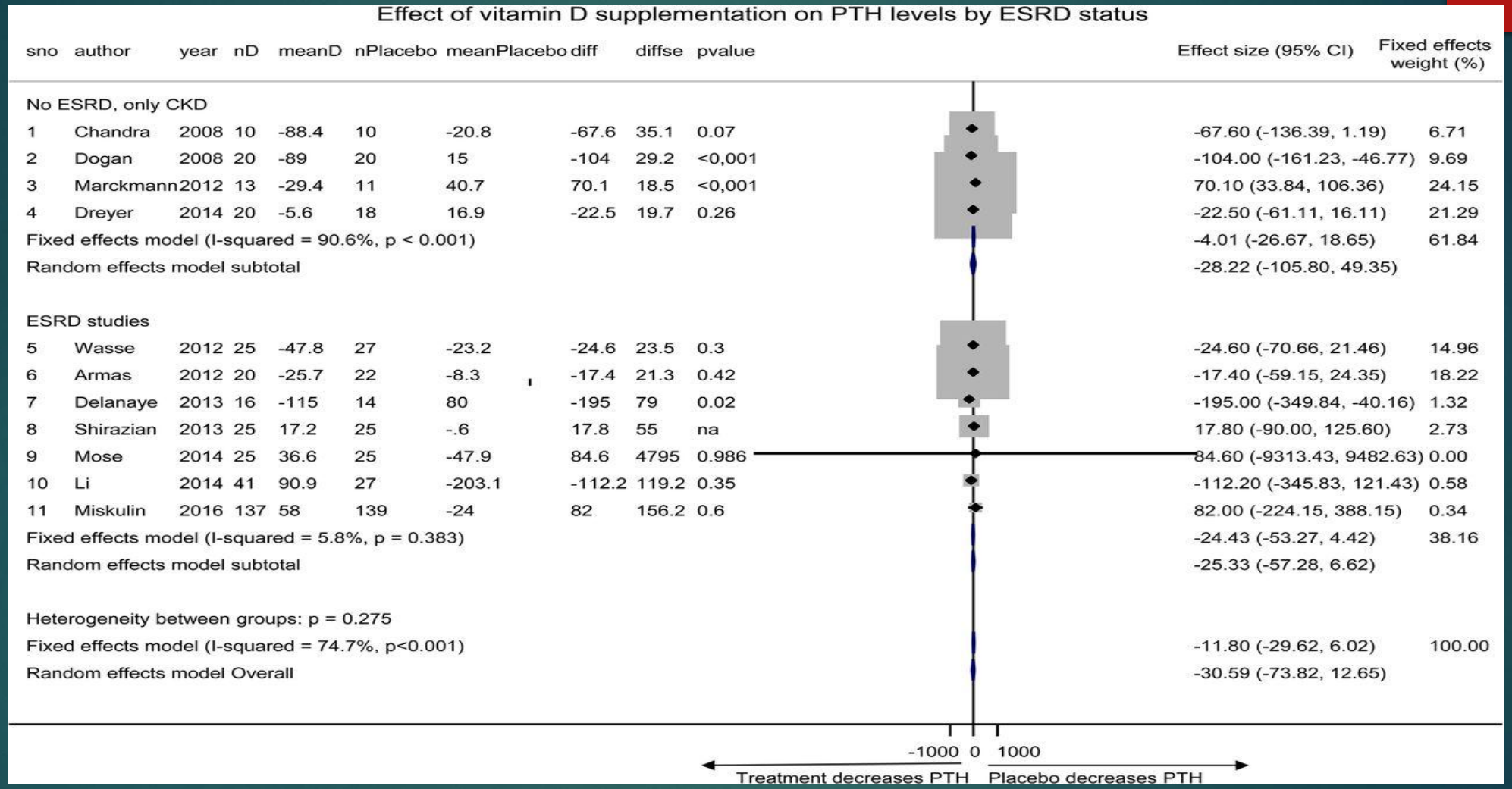


Rajiv Agarwal, and Panagiotis I. Georgianos Nephrol. Dial. Transplant.

2016;31:706-713

NDT Nephrology Dialysis Transplantation

Forest plot depicting the change from baseline in PTH levels in the ‘nutritional vitamin D group’ minus the change from baseline in the ‘placebo group’.



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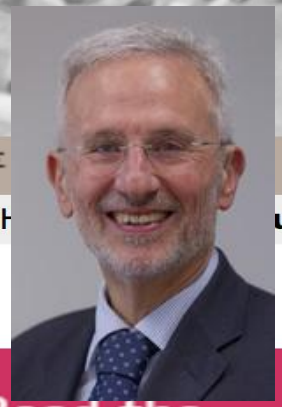

Moderator's view: Vitamin D deficiency treatment in advanced chronic kidney disease: a close look at the emperor's clothes

Carmine Zoccali[1] and Francesca Mallamaci[1,2]

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This Article

Nephrol. Dial. Transplant. (2016) 31 (5): 714-716.
doi: 10.1093/ndt/gfw081

Abstract

Two recent vitamin D supplementation (ergocalciferol) trials in stage G5D CKD patients with vitamin D insufficiency

Pro: Should we correct vitamin D deficiency/insufficiency in chronic kidney disease patients with inactive forms of vitamin D or just treat them with active vitamin D forms?

Table 1.
Vitamin D and derivatives

	Vitamin D2 and derivatives	Vitamin D3 and derivatives
The established vitamin D compounds		
Parent compound	Vitamin D2	Vitamin D3
Synonym	Ergocalciferol	Cholecalciferol
Product of first hydroxylation	25(OH)D2	25(OH)D3
Synonym	Ercalcidiol	Calcidiol
Product of second hydroxylation	1,25-Dihydroxyvitamin D2	1,25-Dihydroxyvitamin D3
Synonym	Ercalcitriol	Calcitriol
The newer vitamin D analogues		
Full term	1-α-Hydroxyergocalciferol	22-Oxacalcitriol
Synonym	Doxercalciferol	Maxacalcitol
Full term	19-Nor-1,25-dihydroxyvitamin D2	F6-1α,25-Dihydroxyvitamin D3
Synonym	Paricalcitol[a]	Falecalcitriol

[a]In some literatures, paricalcitol is considered as the derivative of calcitriol.

Moderator's view: Vitamin D deficiency treatment in advanced chronic kidney disease: a close look at the emperor's clothes

Carmine Zoccali1 and
Francesca Mallamaci1,2

- Ergocalciferol **effectively increases serum 25-hydroxyvitamin** D [25(OH)D].

- The use of **inactive vitamin D forms largely fail to reduce serum PTH and affect various relevant endpoints**, including muscle strength, functional capacity, quality of life and hospitalization.

- **No biological or clinical evidence exists that 25(OH)D may exert meaningful effects in CKD patients who are being treated with active forms of vitamin D.**

Nephrol. Dial. Transplant. (2016)
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Nutritional Vit. D

- **The use of natural vit D2,& D3 will result in**:
  - 1- Raising serum levels of 25(OH)Vit. D definitely yes
  - 2- Raising serum levels of 1,25(OH)Vit. D ?? Yes
  - 3- Suppression of PTH ***NO***
  - 4- Raise s.Ca, and s.Ph ***NO***

How to give Nutritional Vit.D

Vitamin D Repletion in Stage 3 & 4 with Ergocalciferol: KDOQI™ Recommendation 2003

Serum 25(OH)D (ng/mL)	Vitamin D Status	Dose (IU)	Route	Duration (months)	Comment
< 5	Severe deficiency	50,000/wk X 12 wks; then monthly	*po*	6	Assay 25(OH)D after 6 months
		500,000 once	*im*		Assure pt adherence; assay 25(OH)D at 6 months
5-15	Mild deficiency	50,000/wk X 4 wks, then monthly	*po*	6	Assay 25(OH)D after 6 months
16-30	Insufficiency	50,000/mo	*po*	6	

National Kidney Foundation. *Am J Kidney Dis.* 2003;42(4 suppl 3):S1-S201.

CRESCENT 2007

- 4.2.2.
- In adult patient
  dialysis, we sug
  analogs not be
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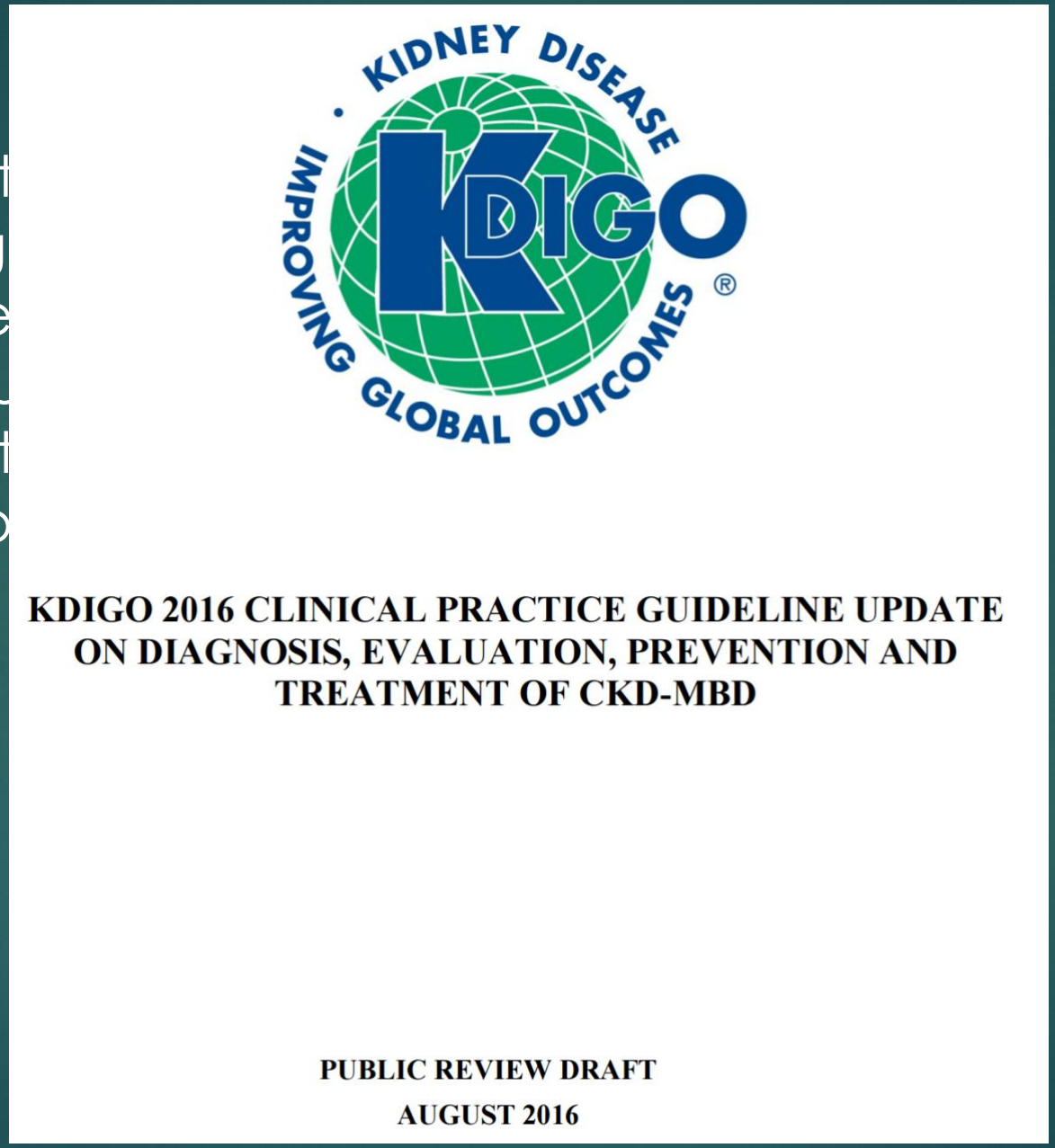
  severe and pro
  Graded)



- 4.2.2.
- In adult patients with CKD Stages 3a-5 not on dialysis, we suggest **calcitriol and vitamin D analogs** not be routinely used. (2C)

- It is reasonable to reserve the use of **calcitriol and vitamin D analogs** for patients with CKD Stages 4-5 with severe and progressive hyperparathyroidism. (Not Graded)

KDIGO 2016 CLINICAL PRACTICE GUIDELINE UPDATE ON DIAGNOSIS, EVALUATION, PREVENTION AND TREATMENT OF CKD-MBD

PUBLIC REVIEW DRAFT

AUGUST 2016

Active vit D

(Calciteriol and Vit D analogues)

Uses of active vit D
(Calciteriol and Vit D analogues)

- 1- to replenish vit D
- 2- to increase Ca levels
- 3- to control PTH
- 4- Skeletal effects
- 5- other
  - CVD, Mortality, Morbidity

Treatment With Activated Vitamin

Table 1: The difference in characteristics of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D.

	Affinity to vitamin D receptor	Serum total concentration	Half-life	Risk of hypercalcemia
25(OH)D	(1)*	9.0–34.0 ng/mL (500)*	480 hrs	Low
$1,25(OH)_2D$	(100–200)*	20–60 pg/mL (1)*	15 hrs	High

*Relative value.

Sprague SM, et al. *Kidney Int*. 2003.

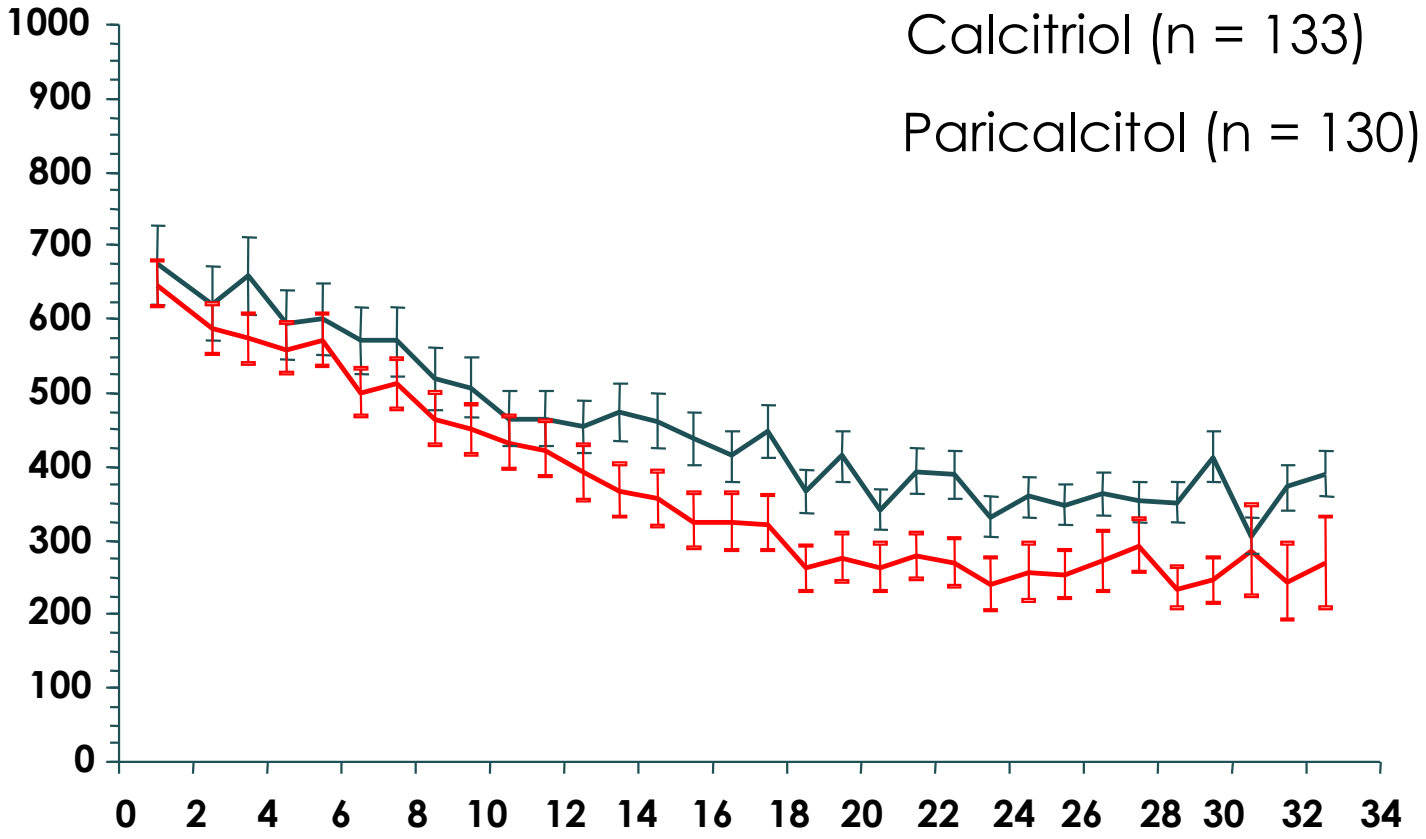
Treatment With Activated Vitamin D

- Goals of activated vitamin D therapy in CKD are : **to correct hypocalcemia and to prevent and treat SHPT**, and to potentially improve health outcomes in CKD.

Treatment With Activated Vitamin D

- **Many small clinical trials** have demonstrated that activated vitamin D agents **lower serum PTH** levels in CKD patients.

Vitamin D Analogs Suppress PTH



Sprague SM, et al. *Kidney Int*. 2003;63:1483-1490.

- One of **the earliest, and best, studies** was done in the **1980s/1990s** , well before the modern era.
- A prospective multicentre study of **176 patients** with a creatinine clearance between 15 and 50 mL/min, **75% had histologic evidence of high-turnover bone** disease at baseline.
- Patients were randomly assigned to placebo or to the synthetic vitamin D analogue, **alfacalcidol (1-hydroxyvitamin D)**, at a dose of 0.25 µg/day, increasing to a maximum of 1 µg/day.
- The **aim of therapy was to raise the serum calcium** concentration to the upper limit of normal for the laboratory [mean 9.8–10 mg/dL (2.45–2.50 mmol/L)], **not in fact primarily to reduce the serum PTH** concentration.

Hamdy NA. *BMJ 1995*
Rix M, *Nephrol Dial Transplant 2004*

- After at least **2 years of follow-up**:
  - **Plasma PTH declined** during the **first 6 months** of alfacalcidol therapy and **then rebounded to pretreatment levels**.
    - In comparison, there was more than a 2-fold increase in PTH levels in the placebo group.
  - Repeat **bone biopsy** showed improvement in **29%** of patients receiving alfacalcidol,
    - whereas the bone disease worsened in 90% of placebo-treated patients.
- **Hypercalcaemia**, was more common in the alfacalcidol group (11 versus 3%).

Hamdy NA. *BMJ 1995*
Rix M, *Nephrol Dial Transplant 2004*

A meta-analysis by Palmer and colleagues reported a **pooled treatment effect for calcitriol on serum PTH levels**:

Systematic literature reviews on vitamin D in patients with CKD

First author, year	Methodology	Number of trials/patients pooled in the analysis	Outcomes tested	Main results
Palmer, 2007 [9]	Meta-analysis	76 studies/3667 CKD patients	Biochemical markers of mineral metabolism, CV and mortality outcomes	Vitamin D compounds did not reduce the risk for death, bone pain, vascular calcification or parathyroidectomy
Haiyang, 2009 [10]	Meta-analysis	6 RCTs/174 CKD patients with sHPT	Suppression of circulating PTH and serum ALP	No significant differences between intermittent intravenous and oral calcitriol in the treatment of secondary hyperparathyroidism for efficacy
Palmer, 2009 [11]	Meta-analysis	60 studies/2773 CKD RD patients	Clinical, biochemical and bone outcomes	Vitamin D compounds lowered serum PTH at the expense of increasing serum calcium and phosphorus
Palmer, 2009 [12]	Meta-analysis	16 studies/894 CKD NRD patients	Biochemical, bone, CV, and mortality outcomes	Vitamin D compounds lowered serum PTH at the expense of increasing serum calcium and phosphorus
Geary, 2010 [13]	Meta-analysis	15 RCTs/369 children with CKD stages 2–5D	Clinical, biochemical and bone outcomes	Vitamin D therapy significantly reduced PTH levels without consistent differences between routes of administration, frequencies of dosing or vitamin D preparations
Wang, 2010 [14]	Meta-analysis	17 studies (8 RCTs and 9 observational studies, among which 5 were prospective studies of CKD RD patients)/315 860 patients	CV disease outcomes	The five studies of patients who received dialysis showed consistent reductions in CV mortality in those who received vitamin D supplements
Kandula, 2011 [15]	Meta-analysis	22 studies (17 observational and 5 RCTs)/1593 patients with CKD NRD, CKD RD and renal transplant recipients	Biochemical outcomes	Vitamin D supplementation (ergocalciferol or cholecalciferol) appears to improve 25(OH)D and 1,25$(OH)_2$D levels while reducing PTH levels without increasing the risk for hypercalcaemia and hyperphosphataemia
Pilz, 2011 [16]	Meta-analysis	10 prospective studies/6853 patients with CKD	Mortality	Higher 25(OH)D circulating levels are associated with significantly improved survival
Cheng, 2012 [6]	Meta-analysis	9 RCTs/832 patients with stage 2–5 CKD	Clinical and biochemical outcomes	Paricalcitol suppresses iPTH and lowers proteinuria without an increased risk of adverse events
Duranton, 2013 [17]	Meta-analysis	14 observational studies/194 932 patients with CKD NRD and CKD RD	Mortality	Therapies with 1,25-dihydroxyvitamin D and analogues are associated with reduced mortality in CKD patients
Han, 2013 [18]	Meta-analysis	9 RCTs/1113 patients with CKD NRD	Clinical and biochemical outcomes	Paricalcitol is effective in lowering PTH in CKD patients and is also effective in lowering proteinuria in diabetic CKD patients with a trend towards hypercalcaemia
Xu, 2013 [19]	Meta-analysis	18 RCTs/1836 patients with CKD at stage 3–5	Reduction in proteinuria, renal function and risk of death	Vitamin D therapy lowered proteinuria without any negative influence on renal function. No superiority for newer versus established vitamin D analogues. No differences regarding the risk of death
de Borst, 2013 [20]	Meta-analysis	6 RCTs/688 patients with proteinuria (84% treated with ACEi or ARB)	Reduction in proteinuria	Paricalcitol and calcitriol both reduced proteinuria
Zheng, 2013 [21]	Meta-analysis	20 observational studies/491 857 CKD patients (CKD RD in 17 of 20 studies)	All-cause and CV mortality	Participants receiving vitamin D had lower all-cause and CV mortality. Patients receiving paricalcitol had a survival advantage over those that received calcitriol
Theodoratou, 2014 [22]	Umbrella review	107 systematic literature reviews, 74 meta-analyses of observational studies of plasma vitamin D concentrations and 87 meta-analyses of RCTs of vitamin D supplementation	Limited to CKD (RCTs/participants): bone pain (4/109), bone fractures (4/181 RD), mortality (4/477 NRD; 5/233 RD), PTX (2/133 RD), hypercalcaemia (7/612 NRD; 5/182 RD), hyperphosphataemia (2/245 NRD; 2/59 RD), risk of requiring dialysis (4/301 NRD)	A clear role of vitamin D does not exist for any outcome, except for hypercalcaemia in CKD NRD

RCT, randomized clinical trial; CKD, chronic kidney disease; CV, cardiovascular; sHPT, secondary hyperparathyroidism; PTH, parathyroid hormone; ALP, alkaline phosphatase; RD, requiring dialysis; NRD, not requiring dialysis; ACEi, angiotensin-converting enzyme inhibitor.

Palmer et al. Meta-analysis:. Ann Intern Med. 2007;147:840-853

PTH

Study, Year (Reference)	Treatment Patients, n	Treatment Mean (SD)	Control Patients, n	Control Mean (SD)	Random Weighted Mean Difference (95% CI)	Weight, %	Random Weighted Mean Difference (95% CI)
Established vitamin D vs. placebo							
Watson et al., 1989 (12)	6	17.93 (14.74)	6	72.93 (31.79)		15.68	−55.00 (−83.04 to −26.96)
Memmos et al., 1981 (11)	26	33.10 (35.90)	24	77.55 (62.81)		15.45	−44.45 (−73.12 to −15.78)
Coen et al., 1994 (48)	30	19.80 (15.40)	30	40.37 (63.80)		17.43	−20.57 (−44.06 to 2.92)
Przedlacki et al., 1995 (54)	13	11.64 (11.49)	12	16.65 (9.99)		22.59	−5.01 (−13.43 to 3.41)
Baker et al., 1989 (13)	7	69.30 (26.40)	6	66.00 (25.30)		15.64	3.30 (−24.85 to 31.45)
Morinière et al., 1985 (42)	12	52.58 (53.35)	15	33.40 (34.98)		13.21	19.18 (−15.81 to 54.17)
Total	94		93			100.00	−17.16 (−36.32 to 2.00)
Test for heterogeneity: chi-square = 21.09 ($P < 0.001$), $I^2 = 76.3\%$							
Newer vitamin D vs. placebo							
Martin et al., 1998 (38)	40	44.66 (73.70)	38	65.12 (27.72)		12.84	−20.46 (−44.94 to 4.02)
Moe et al., 2001 (41)	15	9.34 (10.52)	15	26.58 (24.88)		29.06	−17.24 (−30.91 to −3.57)
Coburn et al., 2004 (32)	27	12.98 (9.68)	28	18.37 (8.69)		58.11	−5.39 (−10.26 to −0.52)
Total	82		81			100.00	−10.77 (−20.51 to −1.03)
Test for heterogeneity: chi-square = 3.73 ($P = 0.15$), $I^2 = 46.4\%$							
Test for overall effect: $Z = 2.17$ ($P = 0.03$)							
Newer vs. established vitamin D							
Hayashi et al., 2004 (36)	35	35.30 (29.70)	38	37.40 (25.52)		100.00	−2.10 (−14.85 to 10.65)
Total	35		38			100.00	−2.10 (−14.85 to 10.65)
Test for heterogeneity: not applicable							
Intravenous vs. oral vitamin D							
Borazan et al., 2003 (78)	16	14.87 (22.00)	18	54.32 (37.40)		10.02	−39.45 (−59.81 to −19.09)
Caravaca et al., 1995 (79)	11	62.59 (39.93)	8	94.71 (50.05)		3.59	−32.12 (−74.07 to 9.83)
Liou et al., 1994 (84)	5	17.70 (14.96)	5	46.64 (11.55)		12.33	−28.94 (−45.51 to −12.37)
Indridason et al., 2000 (81)	19	7.15 (4.73)	17	13.75 (11.36)		20.37	−6.60 (−12.40 to −0.80)
Bacchini et al., 1997 (76)	8	8.80 (6.38)	9	14.96 (9.68)		19.03	−6.16 (−13.88 to 1.56)
Türk et al., 2002 (86)	14	9.57 (5.72)	13	13.09 (6.05)		21.16	−3.52 (−7.97 to 0.93)
Fischer and Harris, 1993 (33)	6	36.96 (16.94)	4	18.70 (6.27)		13.50	18.26 (3.38 to 33.14)
Total	79		74			100.00	−9.47 (−18.14 to −0.80)
Test for heterogeneity: chi-square = 30.62 ($P < 0.001$), $I^2 = 80.4\%$							
Intraperitoneal vs. oral vitamin D							
Gadallah et al., 2000 (87)	18	17.80 (29.80)	16	42.20 (64.20)		0.00	−24.40 (−58.74 to 9.94)
Total	18		16			0.00	−24.40 (−58.74 to 9.94)
Test for heterogeneity: not applicable							
Test for overall effect: $Z = 1.39$ ($P = 0.16$)							
Intermittent vs. daily vitamin D							
Indridason et al., 2000 (81)	19	7.15 (4.73)	17	13.75 (11.36)		41.18	−6.60 (−12.40 to −0.80)
Moe et al., 1998 (40)	10	9.56 (2.72)	8	9.92 (3.54)		57.09	−0.36 (−3.34 to 2.62)
Caravaca et al., 1995 (79)	8	94.71 (50.05)	7	71.61 (39.71)		1.73	23.10 (−22.38 to 68.58)
Total	37		32			100.00	−2.52 (−8.58 to 3.53)
Test for heterogeneity: chi-square = 4.65 ($P = 0.10$), $I^2 = 57.0\%$							

−100 −50 0 50 100

Decreased Parathyroid Hormone Level, *pmol/L* Increased Parathyroid Hormone Level, *pmol/L*

Ca^+ Hypercalcemia

Study, Year (Reference)	Treatment, n/n	Control, n/n	Relative Risk (95% CI)	Weight, %	Relative Risk (95% CI)
Established vitamin D vs. placebo					
Ritz et al., 1995 (46)	0/24	0/21		—	Not estimable
Coen et al., 1994 (48)	0/30	0/30		—	Not estimable
Delmez et al., 2000 (49)	3/8	2/7		23.53	1.31 (0.30 to 5.73)
Watson et al., 1988 (12)	3/6	2/6		26.61	1.50 (0.38 to 6.00)
Rix et al., 2004 (55)	1/16	0/15		5.23	2.82 (0.12 to 64.39)
Hamdy et al., 1995 (14)	10/89	3/87		32.40	3.26 (0.93 to 11.44)
Przedlacki et al., 1995 (54)	2/13	0/12		5.91	4.64 (0.25 to 87.91)
Greenbaum et al., 2005 (45)	5/21	0/26		6.34	13.50 (0.79 to 231.02)
Total	207	204		100.00	2.37 (1.16 to 4.85)
Test for heterogeneity: chi-square = 3.30 ($P = 0.65$), $I^2 = 0\%$					
Newer vitamin D vs. placebo					
Coburn et al., 2004 (32)	1/27	1/28		26.81	1.04 (0.07 to 15.76)
Llach et al., 1998 (59)	3/22	0/13		24.36	4.26 (0.24 to 76.49)
Coyne et al., 2006 (24)	2/107	0/113		22.57	5.28 (0.26 to 108.68)
Akizawa et al., 2004 (29)	27/47	0/26		26.26	30.94 (1.96 to 487.28)
Total	203	180		100.00	5.15 (1.06 to 24.97)
Test for heterogeneity: chi-square = 3.70 ($P = 0.30$), $I^2 = 18.9\%$					
Established vs. newer vitamin D					
Mochizuki et al., 2007 (58)	2/17	1/14		24.51	1.65 (0.17 to 16.33)
Akiba et al., 1998 (63)	3/10	2/11		52.26	1.65 (0.34 to 7.94)
Hayashi et al., 2004 (36)	2/35	1/38		23.23	2.17 (0.21 to 22.91)
Total	62	63		100.00	1.76 (0.56 to 5.47)
Test for heterogeneity: chi-square = 0.04 ($P = 0.98$), $I^2 = 0\%$					
Intravenous vs. oral vitamin D					
Fischer and Harris, 1993 (33)	3/6	5/5		16.45	0.50 (0.22 to 1.11)
Borazan et al., 2003 (78)	2/16	3/18		4.58	0.75 (0.14 to 3.94)
Indridason and Quarles, 2000 (81)	17/19	15/20		51.45	1.19 (0.89 to 1.60)
Quarles et al., 1994 (85)	8/10	5/9		21.92	1.44 (0.74 to 2.79)
Haddad et al., 2004 (80)	4/12	2/11		5.60	1.83 (0.41 to 8.11)
Total	63	63		100.00	1.08 (0.75 to 1.56)
Test for heterogeneity: chi-square = 5.28 ($P = 0.26$), $I^2 = 24.3\%$					
Intermittent vs. daily vitamin D					
Caravaca et al., 1995 (79)	0/8	1/7		1.18	0.30 (0.01 to 6.29)
Klaus et al., 1995 (92)	2/12	3/9		4.40	0.50 (0.10 to 2.40)
Moe et al., 1998 (40)	4/10	4/8		9.94	0.80 (0.29 to 2.24)
Ardissino et al., 2000 (30)	1/30	1/29		1.48	0.97 (0.06 to 14.74)
Indridason and Quarles, 2000 (81)	17/19	15/20		77.94	1.19 (0.89 to 1.60)
Herrmann et al., 1994 (91)	7/21	2/24		5.06	4.00 (0.93 to 17.19)
Total	100	97		100.00	1.15 (0.83 to 1.60)
Test for heterogeneity: chi-square = 5.20 ($P = 0.39$), $I^2 = 3.8\%$					

Ph+ Hyperphosphatemia

Study, Year (Reference)	Treatment Patients, *n*	Treatment Mean (SD)	Control Patients, *n*	Control Mean (SD)	Random Weighted Mean Difference (95% CI)	Weight, %	Random Weighted Mean Difference (95% CI)
Established vitamin D vs. placebo							
Coen et al., 1994 (48)	30	1.45 (0.29)	30	1.38 (0.32)		59.25	0.07 (–0.08 to 0.22)
Morinière et al., 1985 (42)	12	1.81 (0.45)	15	1.62 (0.39)		17.60	0.19 (–0.13 to 0.51)
Przedlacki et al., 1995 (54)	13	1.63 (0.32)	12	1.32 (0.38)		23.16	0.31 (0.03 to 0.59)
Total	55		57			100.00	0.15 (0.01 to 0.29)
Test for heterogeneity: chi-square = 2.33 ($P = 0.31$), $I^2 = 14.1\%$							
Newer vitamin D vs. placebo							
Coburn et al., 2004 (32)	27	1.38 (0.21)	28	1.27 (0.21)		84.61	0.11 (0.00 to 0.22)
Martin et al., 1998 (38)	40	2.00 (0.64)	38	1.75 (0.53)		15.39	0.25 (–0.01 to 0.51)
Total	67		66			100.00	0.13 (0.03 to 0.23)
Test for heterogeneity: chi-square = 0.94 ($P = 0.33$), $I^2 = 0\%$							
Newer vs. established vitamin D							
Hayashi et al., 2004 (36)	35	2.00 (0.52)	38	1.90 (0.52)		100.00	0.10 (–0.14 to 0.34)
Total	35		38			100.00	0.10 (–0.14 to 0.34)
Test for heterogeneity: not applicable							
Intravenous vs. oral vitamin D							
Fischer and Harris, 1993 (33)	6	1.82 (0.32)	4	2.20 (0.40)		3.55	–0.38 (–0.85 to 0.09)
Caravaca et al., 1995 (79)	11	2.10 (0.44)	8	2.20 (0.36)		6.00	–0.10 (–0.46 to 0.26)
Indridason et al., 2000 (81)	19	1.57 (0.39)	17	1.66 (0.43)		10.74	–0.09 (–0.36 to 0.18)
Bacchini et al., 1997 (77)	10	1.69 (0.13)	10	1.78 (0.10)		75.42	–0.09 (–0.19 to 0.01)
Türk et al., 2002 (86)	14	1.87 (0.61)	13	1.87 (0.52)		4.28	0.00 (–0.43 to 0.43)
Total	60		52			100.00	–0.10 (–0.19 to –0.01)
Test for heterogeneity: chi-square = 1.62 ($P = 0.80$), $I^2 = 0\%$							
Intermittent vs. daily vitamin D							
Caravaca et al., 1995 (79)	8	2.20 (0.36)	7	2.32 (0.32)		30.02	–0.12 (–0.46 to 0.22)
Indridason et al., 2000 (81)	19	1.57 (0.39)	17	1.66 (0.43)		49.02	–0.09 (–0.36 to 0.18)
Moe et al., 1998 (40)	10	1.67 (0.58)	8	1.52 (0.29)		20.96	0.15 (–0.26 to 0.56)
Total	37		32			100.00	–0.05 (–0.24 to 0.14)
Test for heterogeneity: chi-square = 1.15 ($P = 0.56$), $I^2 = 0\%$							

ALP

Study, Year (Reference)	Treatment Patients, *n*	Treatment Mean (SD)	Control Patients, *n*	Control Mean (SD)	Random Weighted Mean Difference (95% CI)	Weight, %	Random Weighted Mean Difference (95% CI)
Established vitamin D vs. placebo							
Przedlacki et al., 1995 (54)	13	143.00 (54.40)	12	180.30 (64.00)		12.85	−37.30 (−84.05 to 9.45)
Baker et al., 1989 (13)	7	56.60 (18.30)	6	75.50 (18.80)		68.51	−18.90 (−39.15 to 1.35)
Morinière et al., 1985 (42)	12	115.00 (35.00)	15	131.00 (66.00)		18.63	−16.00 (−54.83 to 22.83)
Total	32		33			100.00	−20.72 (−37.49 to −3.96)
Test for heterogeneity: chi-square = 0.57 (P = 0.75), I^2 = 0%							
Test for overall effect: Z = 2.42 (P = 0.02)							
Newer vitamin D vs. placebo							
Coyne et al., 2006 (24)	101	92.00 (11.30)	107	174.00 (11.00)		37.71	−82.00 (−85.03 to −78.97)
Martin et al., 1998 (38)	40	101.00 (88.00)	38	130.00 (68.00)		30.60	−29.00 (−63.80 to 5.80)
Moe et al., 2001 (41)	15	115.00 (29.00)	15	141.00 (55.00)		31.70	−26.00 (−57.47 to 5.47)
Total	156		160			100.00	−48.03 (−92.20 to −3.86)
Test for heterogeneity: chi-square = 20.73 (P < 0.001), I^2 = 90.4%							
Test for overall effect: Z = 2.13 (P = 0.03)							
Intravenous vs. oral vitamin D							
Caravaca et al., 1995 (79)	11	307.00 (206.00)	8	551.00 (378.00)		3.23	−244.00 (−532.84 to 44.84)
Borazan et al., 2003 (78)	16	198.60 (163.00)	18	211.27 (165.00)		16.27	−12.67 (−123.07 to 97.73)
Indridason and Quarles, 2000 (81)	19	10.60 (4.75)	17	17.80 (18.70)		52.01	−7.20 (−16.34 to 1.94)
Türk et al., 2002 (86)	14	143.00 (120.00)	13	83.00 (48.00)		28.49	60.00 (−8.06 to 128.06)
Total	60		56			100.00	3.42 (−50.11 to 56.95)
Test for heterogeneity: chi-square = 6.30 (P = 0.10), I^2 = 52.4%							
Test for overall effect: Z = 0.13 (P = 0.90)							
Intermittent vs. daily vitamin D							
Caravaca et al., 1995 (79)	8	551.00 (378.00)	7	595.00 (659.00)		0.03	−44.00 (−598.02 to 510.02)
Indridason and Quarles, 2000 (81)	19	10.60 (4.75)	17	17.80 (18.70)		99.97	−7.20 (−16.34 to 1.94)
Total	27		24			100.00	−7.21 (−16.35 to 1.93)
Test for heterogeneity: chi-square = 0.02 (P = 0.90), I^2 = 0%							
Test for overall effect: Z = 1.55 (P = 0.12)							

−100 −50 0 50 100

Decrease in Alkaline Phosphatase, *U/L*

Increase in Alkaline Phosphatase, *U/L*

BoneKEy Reports | Official journal of the International Bone and Mineral Society

Thadhani

BONEKEY REPORTS | **REVIEW**

Vitamin D and chronic kidney disease–mineral bone disease (CKD–MBD)

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Thadhani

Table 3: Summary of vitamin D randomized trials reporting patient level skeletal outcomes in CKD

Study	*Population*	*Number of patients*	*Intervention*	*Results*
Memmos *et al.*[68]	Maintenance hemodialysis	57	Oral calcitriol 0.25–0.5 µg per day for 1–2 years	Improvement in radiological changes of hyperparathyroidism but no change in parathyroidectomy rate
Moriniere *et al.*[71]	Maintenance hemodialysis	27	Oral 1 alpha-OH-vitamin D3 at 0.3–1.0 ug per day for 6 months	No difference in bone pain
Llach *et al.*[76]	Maintenance hemodialysis with mild to moderate secondary hyperparathyroidism	35	Intravenous paricalcitol 0.04 to 0.24 $\mu g kg^{-1}$ three times weekly for 4 weeks	No difference in bone pain
Baker *et al.*[75]	Stage 3–4 CKD	16	Oral calcitriol 0.25–5.0 ug per day for one year	No difference in fracture risk
Delmez *et al.*[77]	Maintenance hemodialysis with mild to moderate secondary hyperparathyroidism	15	Intravenous calcitriol 0.5–2.0 ug three times weekly for 1 year	No difference in fracture or parathyroidectomy rates

Sagar U Nigwe & Ravi I Thadhani, BoneKEy Reports (2014)

CKJ CLINICAL KIDNEY JOURNAL

The most recent version of this article [sfu135] was published on 2015-01-29

The beneficial impact of vitamin D treatment in CKD patients: what's next?

Luigi Francesco Morrone[1] and Mario Cozzolino[2]

+ Author Affiliations

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The beneficial impact of vitamin D treatment in CKD patients: what's next?

Table 1.
Systematic literature reviews on vitamin D in patients with CKD

First author, year	Methodology	Number of trials/patients pooled in the analysis	Outcomes tested	Main results
Palmer, 2007 [9]	Meta-analysis	76 studies/3667 CKD patients	Biochemical markers of mineral metabolism, CV and mortality outcomes	Vitamin D compounds did not reduce the risk for death, bone pain, vascular calcification or parathyroidectomy
Haiyang, 2009 [10]	Meta-analysis	6 RCTs/174 CKD patients with sHPT	Suppression of circulating PTH and serum ALP	No significant differences between intermittent intravenous and oral calcitriol in the treatment of secondary hyperparathyroidism for efficacy
Palmer, 2009 [11]	Meta-analysis	60 studies/2773 CKD RD patients	Clinical, biochemical and bone outcomes	Vitamin D compounds lowered serum PTH at the expense of increasing serum calcium and phosphorus
Palmer, 2009 [12]	Meta-analysis	16 studies/894 CKD NRD patients	Biochemical, bone, CV, and mortality outcomes	Vitamin D compounds lowered serum PTH at the expense of increasing serum calcium and phosphorus
Geary, 2010 [13]	Meta-analysis	15 RCTs/369 children with CKD stages 2–5D	Clinical, biochemical and bone outcomes	Vitamin D therapy significantly reduced PTH levels without consistent differences between routes of administration, frequencies of dosing or vitamin D preparations
Wang, 2010 [14]	Meta-analysis	17 studies (8 RCTs and 9 observational studies, among which 5 were prospective studies of CKD RD patients)/315 860 patients	CV disease outcomes	The five studies of patients who received dialysis showed consistent reductions in CV mortality in those who received vitamin D supplements
Kandula, 2011 [15]	Meta-analysis	22 studies (17 observational and 5 RCTs)/1593 patients with CKD NRD, CKD RD and renal transplant recipients	Biochemical outcomes	Vitamin D supplementation (ergocalciferol or cholecalciferol) appears to improve 25(OH)D and $1,25(OH)_2D$ levels while reducing PTH levels without increasing the risk for hypercalcaemia and hyperphosphataemia
Pilz, 2011 [16]	Meta-analysis	10 prospective studies/6853 patients with CKD	Mortality	Higher 25(OH)D circulating levels are associated with significantly improved survival
Cheng, 2012 [6]	Meta-analysis	9 RCTs/832 patients with stage 2–5 CKD	Clinical and biochemical outcomes	Paricalcitol suppresses iPTH and lowers proteinuria without an increased risk of adverse events

Duranton, 2013 [17]	Meta-analysis	14 observational studies/194 932 patients with CKD NRD and CKD RD	Mortality	Therapies with 1,25-dihydroxyvitamin D and analogues are associated with reduced mortality in CKD patients
Han, 2013 [18]	Meta-analysis	9 RCTs/1113 patients with CKD NRD	Clinical and biochemical outcomes	Paricalcitol is effective in lowering PTH in CKD patients and is also effective in lowering proteinuria in diabetic CKD patients with a trend towards hypercalcaemia
Xu, 2013 [19]	Meta-analysis	18 RCTs/1836 patients with CKD at stage 3–5	Reduction in proteinuria, renal function and risk of death	Vitamin D therapy lowered proteinuria without any negative influence on renal function. No superiority for newer versus established vitamin D analogues. No differences regarding the risk of death
de Borst, 2013 [20]	Meta-analysis	6 RCTs/688 patients with proteinuria (84% treated with ACEi or ARB)	Reduction in proteinuria	Paricalcitol and calcitriol both reduced proteinuria
Zheng, 2013 [21]	Meta-analysis	20 observational studies/491 857 CKD patients (CKD RD in 17 of 20 studies)	All-cause and CV mortality	Participants receiving vitamin D had lower all-cause and CV mortality. Patients receiving paricalcitol had a survival advantage over those that received calcitriol
Theodoratou, 2014 [22]	Umbrella review	107 systematic literature reviews, 74 meta-analyses of observational studies of plasma vitamin D concentrations and 87 meta-analyses of RCTs of vitamin D supplementation	Limited to CKD (RCTs/participants): bone pain (4/109), bone fractures (4/181 RD), mortality (4/477 NRD; 5/233 RD), PTX (2/133 RD), hypercalcaemia (7/612 NRD; 5/182 RD), hyperphosphataemia (2/245 NRD; 2/59 RD), risk of requiring dialysis (4/301 NRD)	A clear role of vitamin D does not exist for any outcome, except for hypercalcaemia in CKD NRD

RCT, randomized clinical trial; CKD, chronic kidney disease; CV, cardiovascular; sHPT, secondary hyperparathyroidism; PTH, parathyroid hormone; ALP, alkaline phosphatase; RD, requiring dialysis; NRD, not requiring dialysis; ACEi, angiotensin-converting enzyme inhibitor.

The beneficial impact of vitamin D treatment in CKD patients: what's next?

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No effects on CVD,
No effect on SHPT

Lowered PTH
Increased Ca& Ph

Reduced CVD
Mortalty,

Reduced CVD
Mortalty& proteinuria

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Lowered PTH & proteinuria

Reduced CVD Mortalty,

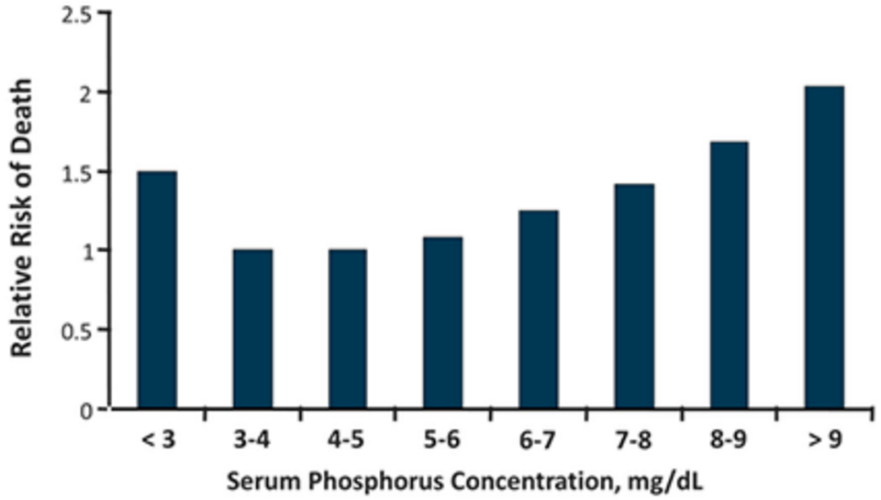
RCT, randomized clinical trial; CKD, chronic kidney disease; CV, cardiovascular; sHPT, secondary hyperparathyroidism; PTH, parathyroid hormone; ALP, alkaline phosphatase; RD, requiring dialysis; NRD, not requiring dialysis; ACEi, angiotensin-converting enzyme inhibitor.

What are the **most prominent** effects of using activated Vit.D in CKD patients?

- 1- Suppression of PTH.
- 2- Increased S phosphorus (Hyperphosphatemia).
- 3- Decreased ALP.
- **4- Increased S Calcium (Hypercalcemia).**

How to use active vit D

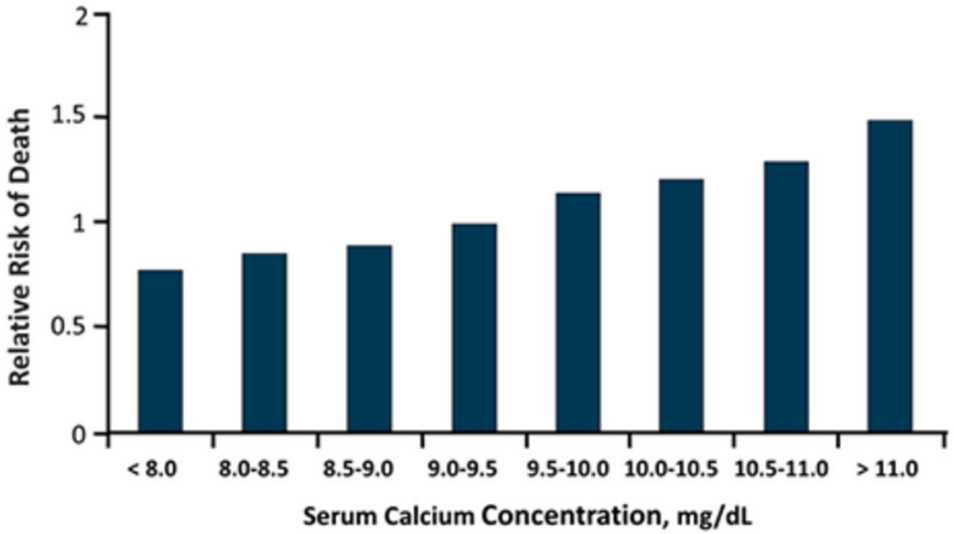
Serum Phosphorus and Risk of Mortality



(Multivariable adjusted)

Block GA, et al. *J Am Soc Nephrol*. 2004;15:2208-2218.[2]

Serum Calcium and Risk of Mortality



(Multivariable adjusted)

Block GA, et al. *J Am Soc Nephrol*. 2004;15:2208-2218.[2]

Jody A. Charnow, Editor

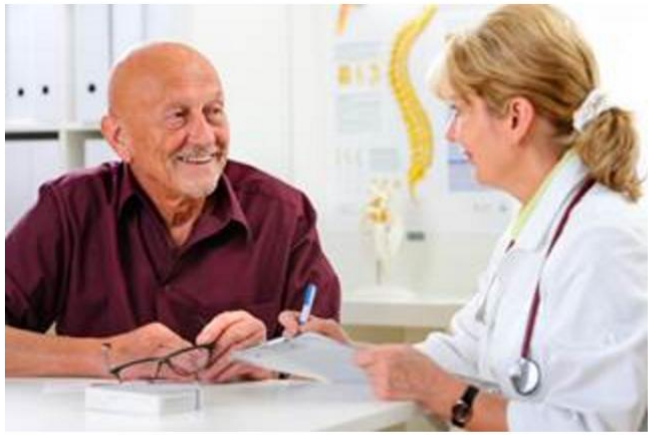
November 17, 2016

GENERAL NEWS

Study Reveals Vitamin D Therapy Effect on Mineral Biomarkers

Share this content:

CHICAGO—Calcitriol and paricalcitol increase fibroblast growth factor 23 and sclerostin levels and decrease certain bone turnover markers while achieving sustained suppression of parathyroid hormone levels in patients with chronic kidney disease and secondary hyperparathyroidism, according to study findings presented at the American Society of Nephrology's 2016 Kidney Week meeting.



Calcitriol and paricalcitol raise levels of fibroblast growth factor 23

A team led by Stuart M. Sprague, DO, University of Chicago, conducted **the post-hoc analysis of PACE study.**

presented at the American Society of Nephrology's November 2016 Kidney Week meeting.

PACE Study

- By week 24, both drugs had significantly decreased iPTH levels as well as (BSAP) and (TRAP) and **significantly increased levels of (FGF 23), and sclerostin**.
- Further studies are required to determine whether increases in FGF 23 may have systemic detrimental effects and increases in sclerostin may contribute to low bone turnover."

How to use active vit D

- **The KDIGO recommended dose in CKD 5d is:**
  - 1- 0.25 ug daily
  - 2- 0.5 ug daily
  - 3- 1 ug daily
  - 4- 1 ug every other day
  - No recomendation

Recommended Vitamin D Dosing in ttt of SHPT

PTH	Ca	P	Ca x P	Calcitriol	Paricalcitol	Doxercalciferol
300 – 600	< 9.5	< 5.5	< 55	IV 0.5 – 1.5 Oral same	2.5 – 5.0 mcg	IV 2 mcg Oral 5 mcg
600 – 1000	< 9.5	< 5.5	< 55	IV 1.0-3.0 Oral 1-4	6.0 – 10 mcg	IV 2 – 4 mcg Oral 5 – 10 mcg
> 1000	< 10	< 5.5	< 55	IV 3.0-5.0 Oral 3-7	10 – 15 mcg	IV 4 – 8 mcg Oral 10 - 20 mcg

- Serum Ca > 10.2 : stop all D, minimize Ca load
- Ca = 9.5-10.2: change to non Ca-containing binder
- Ca < 9.5: continue D or modify with P algorithm
- P > 6.0: stop vitamin D
- P = 5.5–6.0: increase binders, decrease Vitamin D
- P < 5.5: continue or modify using Ca or PTH algorithm

National Kidney Foundation. *Am J Kidney Dis*. 2002;39(Suppl 1):S1-S266.

J Nephrol
DOI 10.1007/s40620-016-0305-6

POSITION PAPERS AND GUIDELINES

Vitamin D in patients with chronic kidney disease: a position statement of the Working Group "Trace Elements and Mineral Metabolism" of the Italian Society of Nephrology

Luigi Francesco Morrone[1] · Pergiorgio Bolasco[2] · Corrado Camerini[3] · Giuseppe Cianciolo[4] · Adamasco Cupisti[5] · Andrea Galassi[6] · Sandro Mazzaferro[7] · Domenico Russo[8] · Luigi Russo[8] · Mario Cozzolino[9]

Table 2 Active vitamin D in pre-dialysis CKD: guidelines

Guidelines	CKD stage	PTH target	Indication to start VDRA
KDOQI 2003 [K/DOQI 2003 Am J Kidney Dis]	3	35–70 pg/ml	Start calcitriol, or alfacalcidol, or doxercalciferol in the presence of 25(OH)D levels <30 ng/ml and PTH levels above the suggested range
	4	70–110 pg/ml	
	5 d	150–130 pg/ml	
KDIGO 2009 [KDIGO (2009) Kidney Int suppls]	3–5	Unknown Maintaining PTH within the normal laboratory range is suggested	Start calcitriol or Vitamin D analogs to raise PTH levels above the normal range despite the correction of low 25(OH)D deficiency, hypocalcemia and hyperphosphatemia
KDIGO 2012 [KDIGO CKD (2012). Kidney Int Suppl]	G3b–G5	Unknown Maintaining PTH within the normal laboratory range is suggested	Start VDRA in the presence of PTH levels raising above the upper normal laboratory range only after ascertained absence of suspected or documented 25(OH)D deficiency, hyperphosphatemia and hypocalcemia
ERBP 2010 [Goldsmith DJA (2010). Nephrol Dial Transplant]	–	–	–
NICE 2014 [NICE guidance. nice.org.uk/cg182]	4–5	–	Start active vitamin D (alfacalcitol or calcitriol) in patients suffering from symptomatic CKD-MBD and GFR <30 ml/min despite an achieved 25(OH)D adequacy

CKD chronic kidney disease, *CKD-MBD* chronic kidney disease and mineral bone disorder, *ERBP* European Renal Best Practice, *KDIGO* Kidney Disease Improving Global Outcomes, *KDOQI* Kidney Disease Outcome Quality Initiative, *NICE* National Institute of Clinical Excellence, *PTH* parathyroid hormone

Luigi Francesco Morrone et al., J Nephrology 2016

- Optimal 25(OH)D levels are still not well defined
- The best therapeutic strategy to replenish 25(OH)D status is unknown.
- Although nutritional and active forms of vitamin D may improve clinical hard endpoints in renal patients, consistent evidence is still lacking in this regard.

Luigi Francesco Morrone et al., J Nephrology 2016

- Active vitamin D therapy should be started in patients in CKD stages 3–5 with
  - **PTH above the normal range** and
  - normal levels of circulating **25(OH)D**
  - **in the absence of hypercalcemia and/or hyperphosphatemia**

Luigi Francesco Morrone et al., J Nephrology 2016

- 4.2.2.
- In adult patients with CKD Stages 3a-5 not on dialysis, we suggest calcitriol and vitamin D analogs not be routinely used. (2C)
- It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD Stages 4-5 with severe and progressive hyperparathyroidism. (Not Graded)

KDIGO 2016 CLINICAL PRACTICE GUIDELINE UPDATE ON DIAGNOSIS, EVALUATION, PREVENTION AND TREATMENT OF CKD-MBD

PUBLIC REVIEW DRAFT

AUGUST 2016

4.2.2. In adult patients with CKD Stages 3a-5 not on dialysis, we suggest calcitriol and vitamin D analogs not be routinely used (*2C*). It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD Stages 4-5 with severe and progressive hyperparathyroidism (*Not Graded*). In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range (*Not Graded*).	4.2.2. In patients with CKD stages 3–5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (*2C*).	Recent RCTs of vitamin D analogs failed to demonstrate improvements in clinically relevant outcomes but did demonstrate increased risk of hypercalcemia.

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Active vitamin D analogs use

- Treatment with either calcitriol or a synthetic vitamin D analog should be given **only if**:
  - the serum phosphate is in the normal range and
  - the corrected serum total calcium concentration is <9.5 mg/dL.

- Vitamin D therapy should also be discontinued **if**:
  - intact PTH levels become persistently low, or
  - the serum level of corrected total calcium exceeds 10.2 mg/dL.

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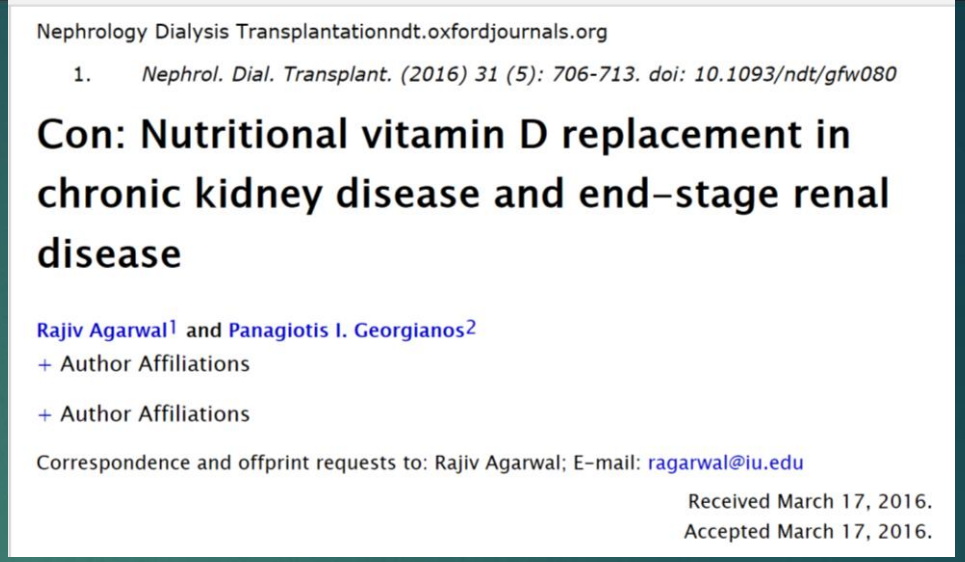
Vit. D Dilemma


Nephrology Dialysis Transplantationndt.oxfordjournals.org

1. *Nephrol. Dial. Transplant. (2016) 31 (5): 706-713. doi: 10.1093/ndt/gfw080*

Con: Nutritional vitamin D replacement in chronic kidney disease and end-stage renal disease

Rajiv Agarwal[1] and Panagiotis I. Georgianos[2]

+ Author Affiliations

+ Author Affiliations

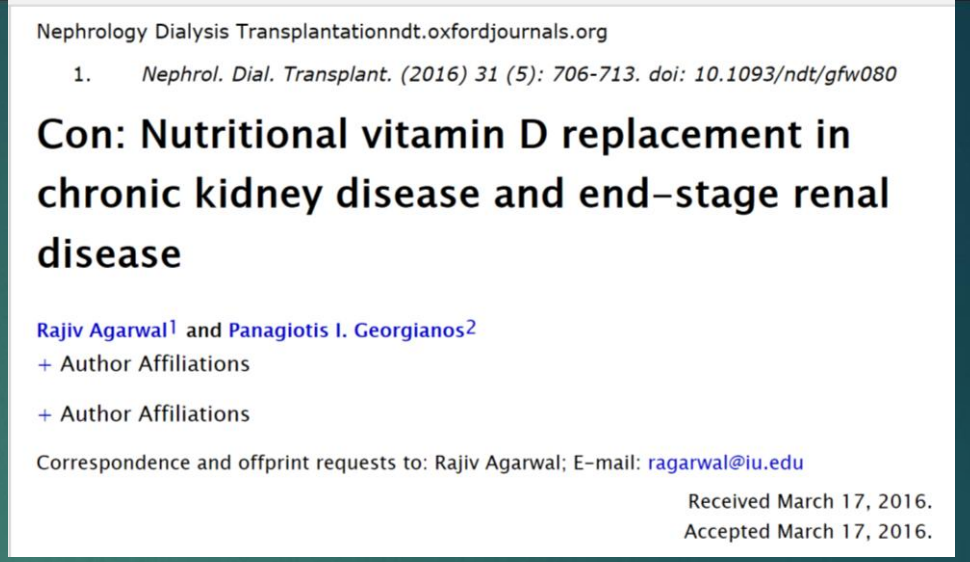
Correspondence and offprint requests to: Rajiv Agarwal; E-mail: ragarwal@iu.edu

Received March 17, 2016.
Accepted March 17, 2016.

- There is **safety issues** about the injudicious use of active vitamin D forms, pointing to the **risk of hypercalcemia and vascular calcification**, a risk that seems to be minimal or absent with inactive vitamin D.

Rajiv Agarwal, and Panagiotis I. Georgianos, Nephrol. Dial. Transplant. (2016)

Vit. D Dilemma



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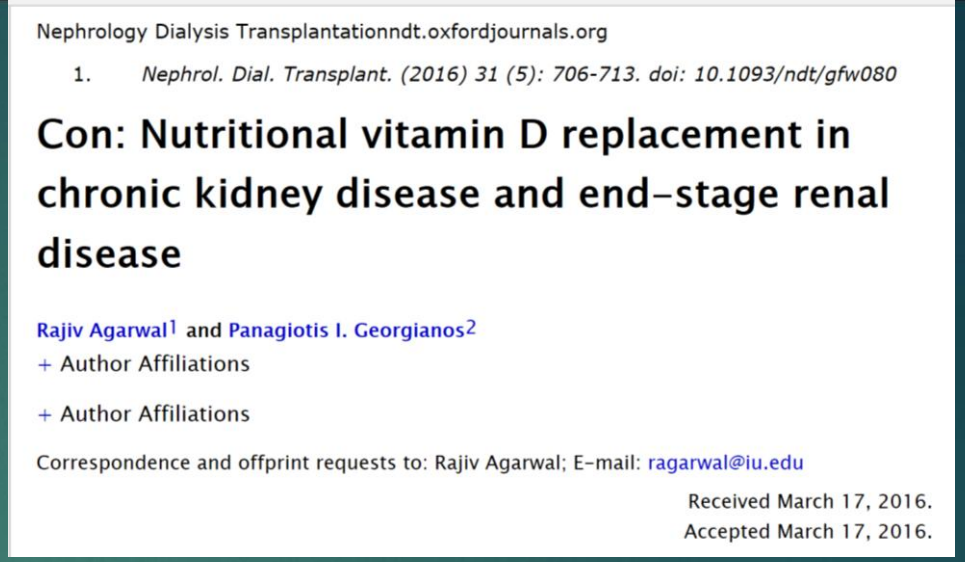
- **With appropriate attempts to control phosphate, calcium and PTH using diet, dialysis, phosphate binders and 'natural' vitamin D species, if the PTH is still deranged, and we feel compelled to continue to try to reduce its serum concentration, we can then swap to active Vit. D**

Rajiv Agarwal, and Panagiotis I. Georgianos, *Nephrol. Dial. Transplant. (2016)*

Vit. D Dilemma



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Received March 17, 2016.
Accepted March 17, 2016.

- On the other hand, **correction** of low Vit. D with the use of **nutritional vitamin D** supplements in people with CKD is **not justified** by the currently available evidence.
- Agarwal, thinks that it would be fair to comment that we do not have the answers to any of these questions.

Rajiv Agarwal, and Panagiotis I. Georgianos, Nephrol. Dial. Transplant. (2016)

Pro: Should we correct vitamin D deficiency/insufficiency in chronic kidney disease patients with inactive forms of vitamin D or just treat them with active vitamin D forms?

ndt
Nephrology Dialysis Transplantation

David J.A. Goldsmith

- **The common practice to use high and fixed doses of synthetic vitamin D, should be re-evaluated.**

David J.A. Goldsmith, NDT. (2016)31 (5): 698-705.

Pro: Should we correct vitamin D deficiency/insufficiency in chronic kidney disease patients with inactive forms of vitamin D or just treat them with active vitamin D forms?

ndt
Nephrology Dialysis Transplantation

David J.A. Goldsmith

- While there are a number of studies that report the impact of vitamin D supplementation on serum vitamin D concentrations, there has been much less focus on hard or semi-rigid clinical end point analysis (e.g. fractures, hospitalizations).

David J.A. Goldsmith, NDT. (2016)31 (5): 698-705.

Pro: Should we correct vitamin D deficiency/insufficiency in chronic kidney disease patients with inactive forms of vitamin D or just treat them with active vitamin D forms?

ndt
Nephrology Dialysis Transplantation

David J.A. Goldsmith

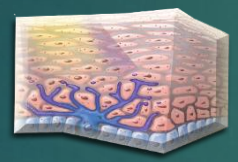
- It is disappointingly true to say that even in 2016 there is a remarkable paucity of evidence concerning the clinical benefits of vitamin D supplementation to treat patients with stage 3b–5 CKD.

David J.A. Goldsmith, NDT. (2016)31 (5): 698-705.

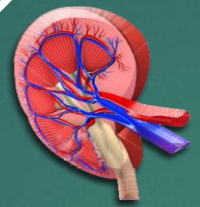
Physiologic Effects of Vitamin D Throughout the Body

25(OH)D
Major Circulating Metabolite

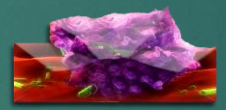
Keratinocytes



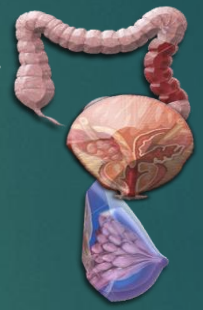
Kidney



Macrophages



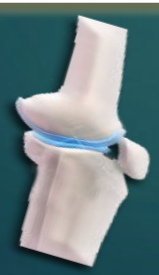
Colon
Prostate
Breast, etc.



$1,25(OH)_2D$
Biologically Active

Calcium and Phosphorus Homeostasis

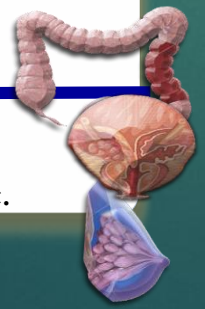
Bone Health



Growth & Regulation

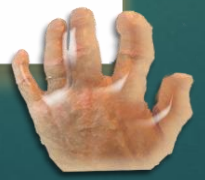
Antiproliferation
Prodifferentiation
Apoptotic
Anti-angiogenic

Prostate,
Colon,
Breast Cancers etc.



Immunomodulatory Effects

Multiple Sclerosis
Type 1 Diabetes
(via ß-islet cell destruction)
Psoriasis
Rheumatoid Arthritis
Inflammatory Bowel Disease
Periodontal Disease



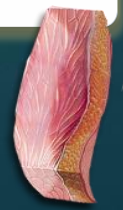
Cardiovascular Effects

Renin-Angiotensin Regulation

Decreased Risk for:
Hypertension
Type II Diabetes
(via stimulation of pancreatic insulin production)
Heart Failure

Neuromuscular Effects

Muscle Mass
Muscle Strength
Better Balance



Adapted from: Holick MF. *Mayo Clin Proc*. 2006;81:353-373.

But in CKD

- **To D or not to D**
- **THAT'S THE QUESTION**

But in CKD

- **To D and how to D**
- **THAT'S ANOTHER QUESTION**