

ProRenal QD / **ProRenal**[®]
With Omega-3 VITAL

The Importance of Nutritional Vitamin D in CKD

PARTNERS IN EDUCATION

Nephroceuticals

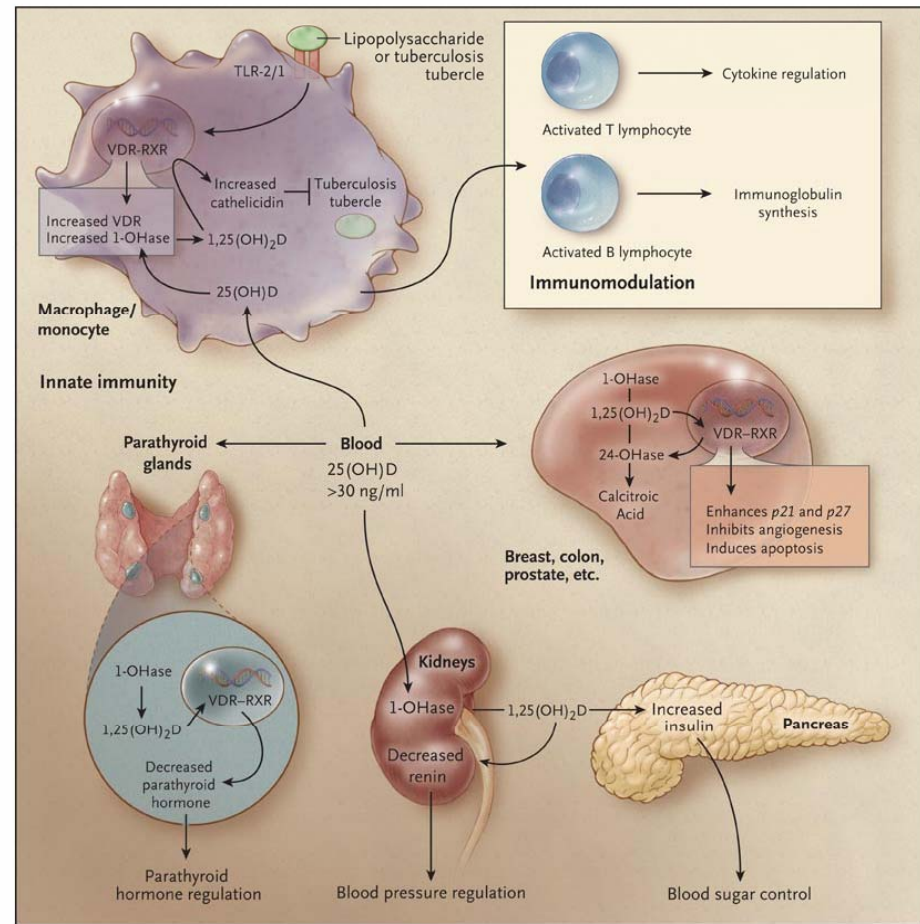
 National Kidney
Foundation

Nephroceuticals

Background

Non-skeletal Actions of Vitamin D

- Vitamin D receptors are present in a wide variety of tissues, resulting in important health implications



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

Definition of Deficiency and Insufficiency

25(OH) Vitamin D levels:

Over 30ng/ml: Sufficient

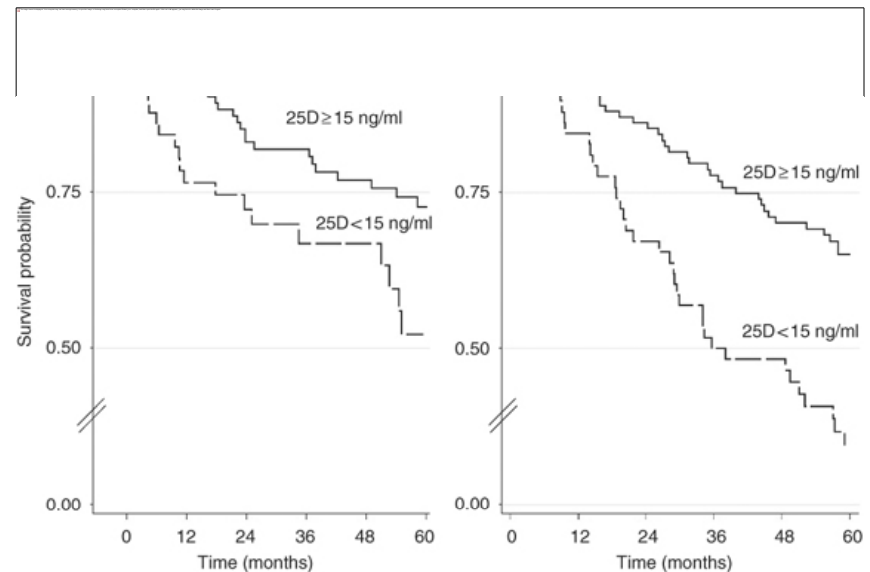
15-30ng/ml: **INSUFFICIENT**

Under 15ng/ml: **DEFICIENT**

Prevalence and Complications of Low Vitamin D levels

Low Vitamin D Levels Are Common and Linked to Poor Outcomes in CKD

- Prevalence of Vitamin D deficiency or insufficiency in CKD: 71-88%^{1,2}
- Low 25(OH) Vitamin D levels associated with progression to dialysis and death³



1. LaClair, R Am J Kidney Dis. 2005 Jun;45(6):1026-33 2. Kooienga, L. Am J Kidney Dis. 2009; 53(3):408-416 3. Ravani, P. Kidney Int 2009; 75:88-95

Prevalence of 25(OH)D deficiency in **CKD 5D**

From a variety of studies, prevalence of vitamin D deficiency/insufficiency ranges from **70% to over 90%** ^{1,2,3,4}

1. Tokmak, F. Nephrol Dial Transplant (2008) 23: 4016–4020. 2. Jean, G. Nephrol Dial Transplant (2008) 23: 3670–3676 3. Saab, G. Nephron Clin Pract 2007;105:c132–c138. 4. Shah, N. Perit Dial Int 2005;25(4):362

Low Vitamin D Levels Associated with Increased Mortality in ESRD

Table 4a | ORs of risk of death within 90 days of initiating chronic hemodialysis according to baseline 25D levels

25D	< 10 ng/ml n=187	10–30 ng/ml n=594	> 30 ng/ml n=203
<i>All-cause mortality</i>			
Age, gender, race-adjusted	1.9* (1.3–2.9)	1.4* (1.0–2.0)	1.0 (REF)
Multivariate-adjusted	1.6* (1.0–2.4)	1.3 (0.9–1.8)	1.0 (REF)
<i>Cardiovascular mortality</i>			
Age, gender, race-adjusted	1.9* (1.0–3.4)	1.8* (1.2–2.9)	1.0 (REF)
Multivariate-adjusted	1.6 (0.8–3.0)	1.6* (1.0–2.6)	1.0 (REF)

25D, 25-hydroxyvitamin D; OR, odds ratio.

*P<0.05 compared with the reference group.

REF refers to the reference group for these analyses.

Possible mechanism: low calcidiol levels inversely associated with coronary calcifications in CKD² and arterial and endothelial dysfunction in ESRD³

1. Wolf, M. *Kid Inter* 2007; 72(8) 1004. 2. de Boer, I. *J Am Soc Neph* 2009; 20:1805. 3. London, G. *J Am Soc Nephrol* 18: 613–620, 2007

Low Vitamin D Levels Are **Nearly Universal** in Recipients of Renal Transplants

- **Nearly 90%** were deficient or insufficient at time of transplant ¹
- Deficiency/insufficiency **persists over time, and exists across ethnicities**
 - Patients with transplants over 1 year continued to have high rates of hypovitaminosis D²
 - Over 90% of African American transplant recipients were insufficient³
 - 81% of Danish cohort were either deficient or insufficient ⁴

1. Sadlier, D. Clin Transplant 2007;21:683. 2. Stavroulopoulos, A. Am J Transpl 2007;7:2546. 3. Tripathi, S. Transplantation 2008;85(5):767 4. Ewers, B. Am J Clin Nutr 2008;87:431

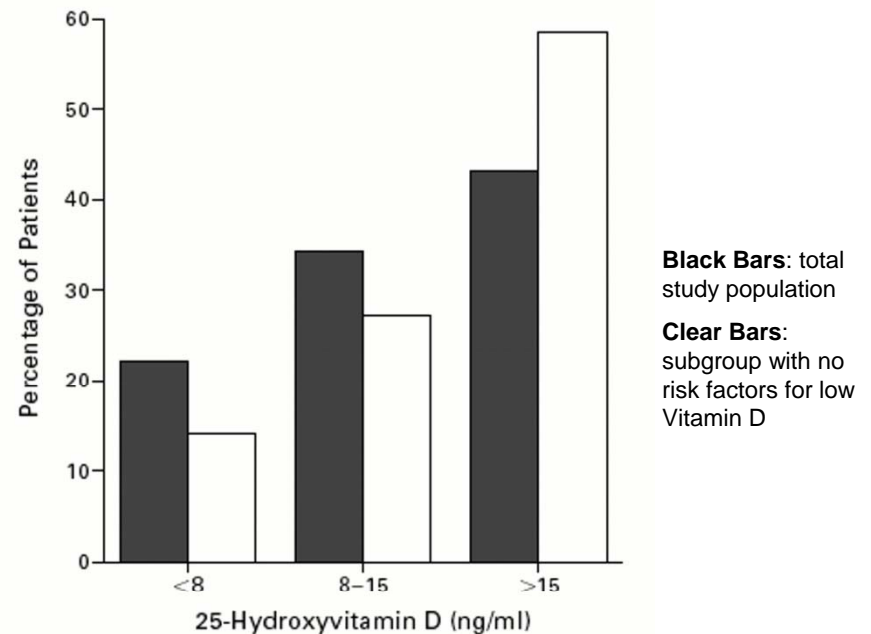
Low Vitamin D Levels are Potentially Linked to **Poor Health Outcomes** in Renal Transplantation

- Low 25(OH) vitamin D levels pre-transplant associated with **increased risk of cancer**¹
- Local activation of 25(OH)Vitamin D by macrophages and dendritic cells may modulate **T-cell immune response**²
- May aggravate **secondary hyperparathyroidism** post-transplant³

1. Ducloux, D. Transplantation 2008; 85(12):1755. 2. Adams, J Ann NY Acad Sci2007;1117:94 3. Tripathi, S. Transplantation 2008;85(5):767

Hypovitaminosis D Commonly Seen in Hospitalized Patients

- In 290 general medicine inpatients, over 50% were *deficient*¹
- Among ICU patients, only 7% were sufficient, with 17% having *undetectable levels*²



Thomas, M. NEJM, 1998

Thomas, M. N Engl J Med 1998;338:777. 2. Lee, P. N Engl J Med 2009;360:1912

Treatment of Vitamin D Insufficiency/Deficiency

Active Vitamin D Does **NOT** Treat “Nutritional” Vitamin D Deficiency

- 1-alpha hydroxylase present in many tissues, including keratinocytes, macrophages, and brain¹
- Extra-renal 1-alpha hydroxylase can produce active vitamin D to act in an **autocrine or paracrine manner**¹
- Half-life of active Vitamin D is **much shorter** than 25(OH) vitamin D, and blood levels are **substantially lower**

Need to provide fuel for the extra-renal 1-alpha hydroxylase for tissue-specific production of active vitamin D

1. Tokmak, F. Nephrol Dial Transplant (2008) 23: 4016–4020

Cholecalciferol (D3) is Superior to Ergocalciferol (D2)

- Greater increases in 25(OH) vitamin D levels with cholecalciferol¹
- Cholecalciferol maintains higher levels of 25(OH)-vitamin D over time²
- Many successful trials, including all successful fracture trials, used D3³
- Greater efficacy may be related to higher affinities to hepatic 25-hydroxylase, DBP, VDR, and differences in deactivation⁴

1. Trang H, Am J Clin Nutr 1998;68:854. 2. Armas LA. J Clin Endocrinol Metab 2004;89:5387–91 3. Bischoff-Ferrari HA. JAMA 2005;293:2257. 4. Houghton, L. Am J Clin Nutr 2006;84:694

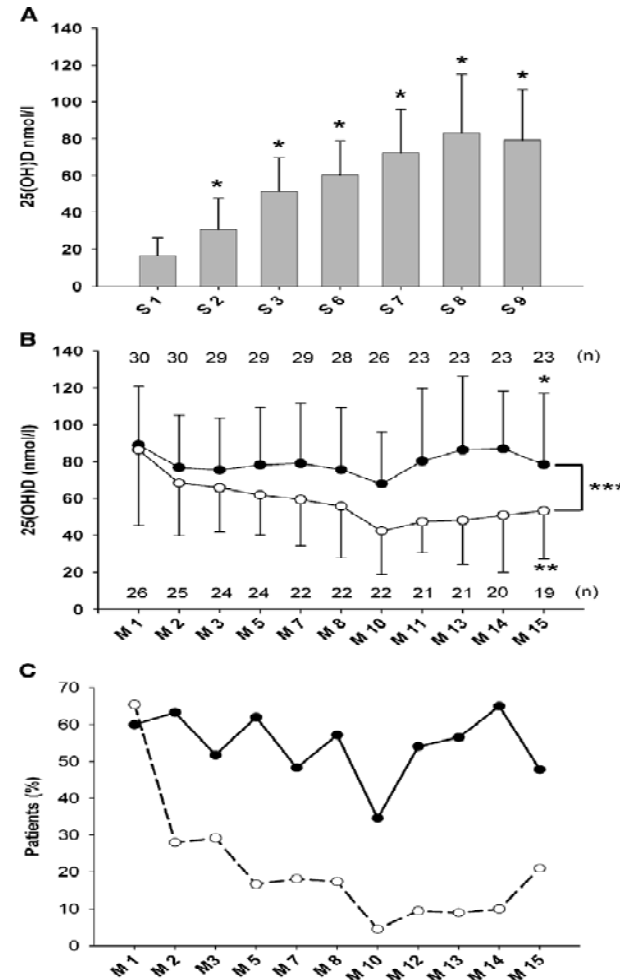
Cholecalciferol Can Raise Vitamin D levels in CKD

- Kooienga, et al¹ – **800IU/day**
 - 610 Stage 3 **CKD** patients
 - Nearly 50% achieved Vitamin D sufficiency
 - Resulted in reduction in PTH
- Rucker, et al² – **1000IU/day**
 - 128 **Stage 3-5 (non-dialysis) Canadian** CKD patients, prospective controlled trial
 - Mean 25(OH)D levels rose 10 ng/ml

1. Kooienga, L.. Am J Kidney Dis 2009; 53(3):408. 2. Rucker, D. J Nephrol 2009; 22:75

Maintenance dose may be important in ESRD

- Prospective study of 64 patients
- Deficiency present in 95% of patients
- Treatment
 - Replenishment phase: 20,000units cholecalciferol weekly X 9 months
 - Maintenance: 20,000units monthly for 15 mo
- Results: mean 25(OH)D levels increased; those receiving maintenance doses maintained adequate 25(OH)D levels
- 3 patients had their active D dose held and then resumed at lower levels

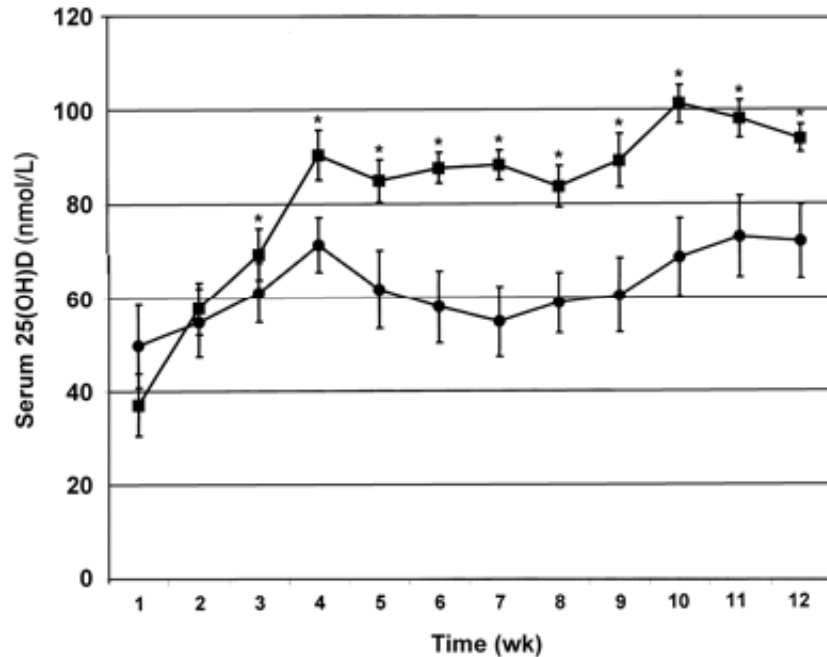


Cholecalciferol Can Be Safely Given with Active Vitamin D in ESRD

- **Tokmak, 2008¹**
 - 64 HD patients, 95% deficient in 25(OH)D
 - 3 patients developed transient hypercalcemia, resolved with temporary cessation of active vitamin D
- **Jean, 2008²**
 - Mean dose 640 IU 25-hydroxycholecalciferol
 - 3% developed hypercalcemia, resolved with discontinuation of active Vitamin D
 - More patients reached KDOQI calcium, phos targets and albumin increased
- **Saab, 2007**
 - No hypercalcemia attributed to supplementation
 - ?Epo sparing effect

1. Tokmak, F. Nephrol Dial Transplant (2008) 23: 4016–4020. 2. Jean, G. Nephrol Dial Transplant (2008) 23: 3670–3676 3. Saab, G. Nephron Clin Pract 2007;105:c132–c138

Evidence For 1000IU Cholecalciferol



Mean (\pm SEM) serum 25-hydroxyvitamin D [25(OH)D] concentrations increased in **subjects who ingested 1000 IU vitamin D(5)**

Fracture prevention: 800IU/day¹

Fall prevention: 800IU/day²

Cancer prevention: 1100/day³

Improved 25(OH)-D levels in
CKD: 1000IU⁴

Canadian Cancer society
recommendations: 1000 IU/day

**Use of doses over 500IU/day
associated with lower mortality⁶**

1. Chapuy, M. N Engl J Med 1992; 327:1637 2. Bischoff-Ferrari, H. Am J Clin Nutr 2006;84:18–28. 3. Lappe, J. Am J Clin Nut 2007; 85(6):1586.
4. Rucker, D. J Nephrol 2009; 22:75. 5. Tangpricha, V. Am J Clin Nut 2003; 77: 1478. 6. Autier, P. Arch Int Med 2007; 167(16):1730

What KDOQI says about **Vitamin D**

1. CKD patients are much more likely to have low levels of 25(OH)D
2. Treatment and prevention of vitamin D insufficiency in CKD Stage 3&4 reduces frequency and severity of secondary hyperparathyroidism
3. Vitamin D deficiency or insufficiency can be prevented by vitamin D2 or D3 supplementation

“Once patients are replete with vitamin D, continued supplementation with a **vitamin-D-containing multi-vitamin preparation should be used ...”**

What **KDIGO** says about Vitamin D

“In patients with **CKD stages 3–5D**, we suggest that **25(OH)D (calcidiol) levels might be measured... We suggest that vitamin D deficiency and insufficiency be corrected...**”

“In patients with **CKD stages 3–5 not on dialysis**, we suggest that patients with levels of **intact PTH (iPTH) above the upper normal limit** are first evaluated for ... vitamin D deficiency. It is reasonable to correct these abnormalities with ... **native vitamin D.**”

“In patients with **CKD stages 1–5T**, we suggest that **25(OH)D (calcidiol) levels might be measured...** In patients with CKD stages 1–5T, we suggest that **vitamin D deficiency and insufficiency be corrected...**”