The ABC's on choosing the right vitamin D…

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RPN Day, March 2010

Objectives

- Pathophysiology of hypovitaminosis D
- Vitamin D compounds
- Traditional effects of vitamin D
- Nontraditional effects of vitamin D

1. Is your program measuring 25(OH)D level?

2. Is your program treating nutritional vitamin D insufficiency or deficiency? Cholecalciferol vs. Ergocalciferol?

3. Are you taking vitamin D?

Case--Mrs. M.B.

- 56 y/o ♀, weight: 52kg, height: 160 cm
- RFA: Hip fracture
- PMHx: CKD Stage 5 (started hemodialysis 6 months ago), Type 1 DM (nephropathy, peripheral neuropathy, retinopathy), stable A.Fib.
- Allergy: NKDA

Case--Mrs. M.B.

- Current medications:
  - **Alfacalcidol, 0.25 mcg po 3x/week**
  - Atorvastatin, 20 mn po OD
  - EC ASA, 81 mg po OD
  - **Calcium acetate, 1 tab po BID with lunch an supper**
  - Furosemide, 80 mg po BID
  - Gabapentin, 100 mg po QAM and 200 mg po QHs
  - Metoprolol, 50 mg po BID
  - Ramipril, 10 mg po QD
  - Ranitidine, 150 mg po OD
  - Replavite, 1 tab po OD
  - Warfarin, dose according to INR
  - Insulin glarginine, 20 IU sc Qbreakfast
  - Insulin lispro, 5-10 IU sc TID before meals
  - Ferrlecit, 125 mg IV Qmonth
  - Darbepoitin, 30 mcg IV Qweek
  - Hydromorphone, 1-2 mg po Q2 Hrs PRN
  - Enoxaparin, 30 mg sc OD
  - **Cholecalciferol, 800 IU po QD**

Case--Mrs. M.B.

- Social Hx: Ø alcohol; Ø smoker
- Family Hx:
  - Dad → MI (died @ 60 years old)
  - Mom → HTN & DM2

Case--Mrs. M.B.

- **Labs at last HD blood work**
  - **Heme:**

WBC	Neut	Hgb	HCT	Tsats	Ferritin	Plt
8.7	5.9	104	0.31	0.25	450	211

  - **Chem:**

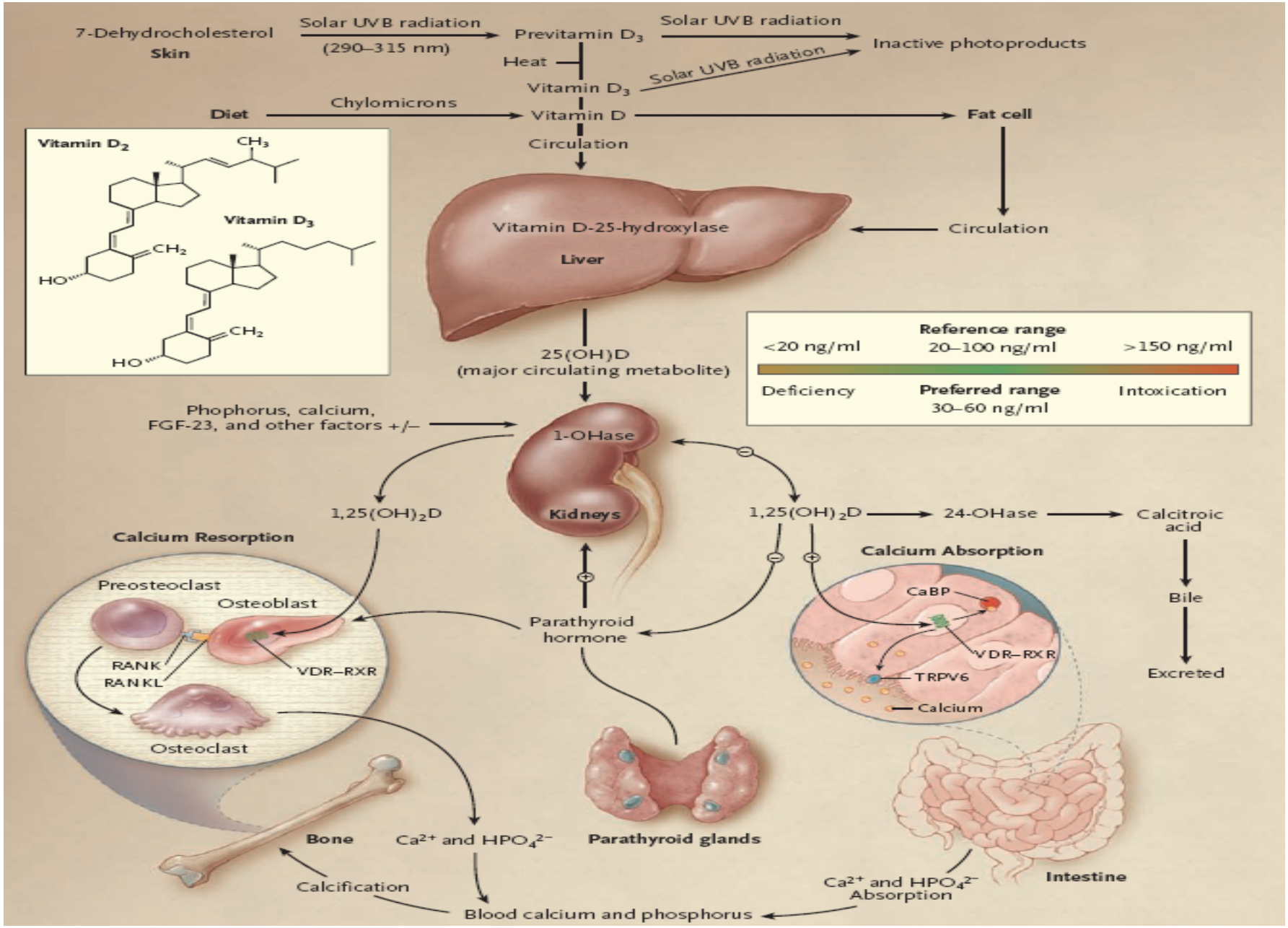
Na	K	Cl	Ca	PO_4	BUN	Scr	eGFR	Gluc
136	4.4	99	2.26	1.3	20	358	11	6.1

  - **Others:**

Alb	iPTH	HbA1c
38	**27.6**	7.6

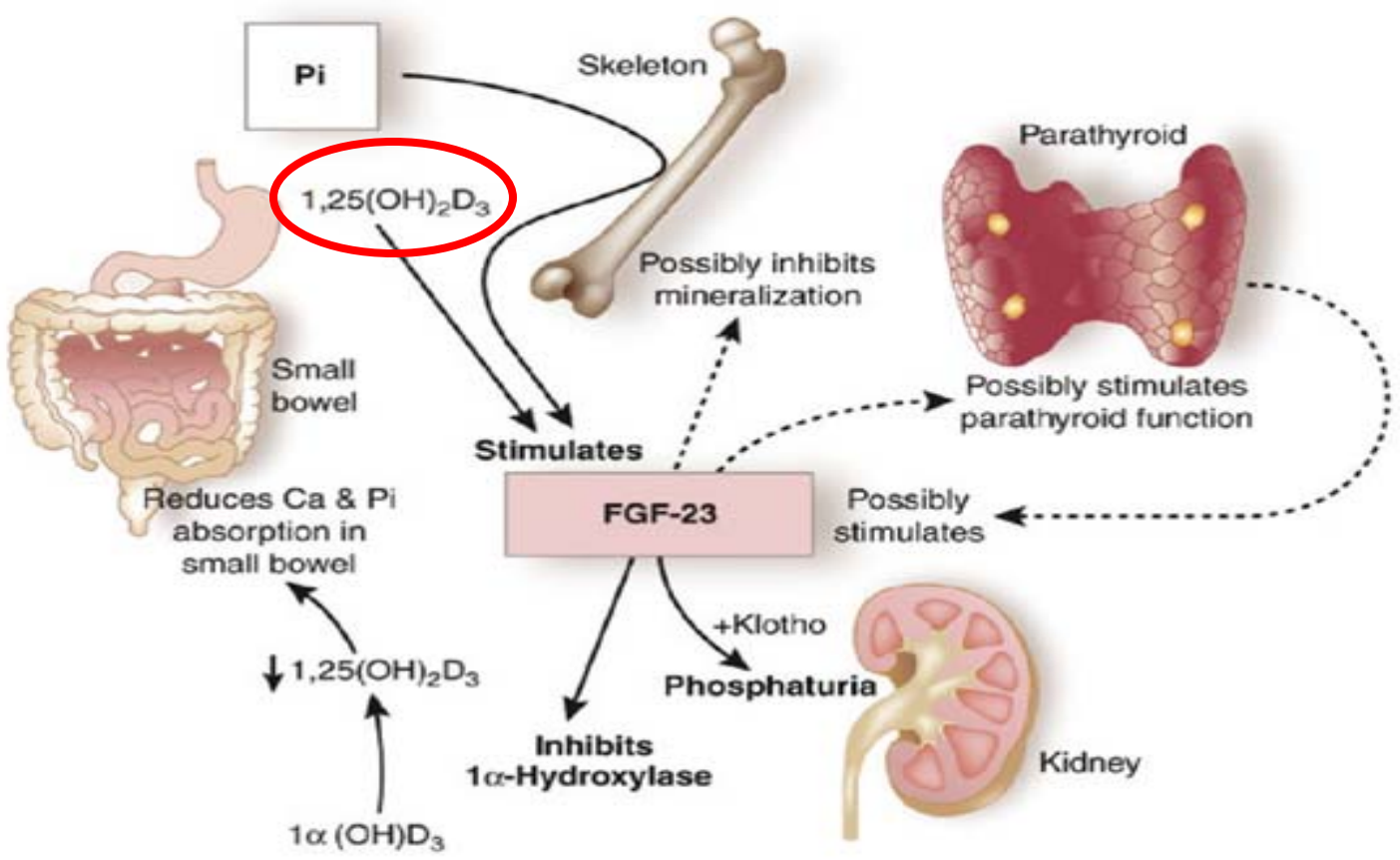
Intervention?

How is vitamin D metabolized?



Holick MF. NEJM 2007;357: 266-81.

CKD-BMD new era…



Emmett M. Kidney Int 2008;73:3-5.

What is the definition of vitamin D deficiency?

Hypovitaminosis D

- No consensus on optimal level of 25(OH)vitD
  - Vit D deficiency usually defined as < 25-50 nmol/L (10-20 ng/mL)
  - Vit D insufficiency usually defined as < 75-100 nmol/L (30-40 ng/mL)
  - Hypovitaminosis D $\Rightarrow$ Vit D insufficiency and vit D deficiency

- 1 billion of people worldwide have hypovitaminosis D
  - 20-50% of general population
  - 40-100% of U.S. and European community elderly
  - > 50% of postmenopausal women taking osteoporosis treatment
  - 30-50% of teenager and young adults
  - Results vary according to race, geographic situation, season, age, other co-morbidities

Holick MF. NEJM 2007; 357: 266-81.

Why not measuring the 1,25(OH)2vitD level?

Vitamin D levels

- 25(OH)D level
  - Best measure ($t_{1/2}$~3 weeks)
  - Measure collectively 25(OH)D_3 and 25(OH)D_2
  - 25(OH)D is main storage form and circulating metabolite
  - Between lab and inter-assay variation reported > 35%
  - Seasonal variation

- 1,25$(OH)_2$D level
  - Less reliable ($t_{1/2}$~8 hours)
  - Assay not standardized
  - Influenced by exogenous administration of VDRAs
  - No data related to outcome

Johal M. Clin J Am Soc Nephrol 2009; 4: 1508-14.

What are the causes of hypovitaminosis D?

Hypovitaminosis D

Causes	Examples
↓ skin synthesis	Sunscreen, skin pigment, aging, season, latitude, skin grafts
↓ bioavailability	Malabsorption (Rx ↓ cholesterol absorption), obesity
↑ catabolism	Anticonvulsant, steroids, HAART, antirejection Rx
Breast-feeding	
↓ synthesis of 25(OH)vit D	Liver failure (>90% dysfunction)
↑ urinary loss of 25(OH)vit D	Nephrotic syndrome
↓ synthesis of 1,25(OH)$_2$vitD	**CKD**

Holick MF. NEJM 2007; 357: 266-81.

Hypovitaminosis D in CKD

- Dietary restriction and malabsorption
- ↓ renal proximal cell ⇒ ↓ renal 1(OH)ase enzyme
- Hyperphosphatemia, metabolic acidosis, uremia ⇒ ↓ing 1(OH)ase activity
- ↓ skin production of cholecalciferol
- Proteinuria ⇒ loss of 25(OH)D bound to DBP.

Wolfe. Kidney International 2007; 72: 1004-13.

Hypovitaminosis D in CKD

Reference	Sample	Location	Serum 25(OH)D (ng/mL)	Prevalence of Serum 25(OH)D <30 ng/mL	Factors Associated With 25(OH)D
Ishimura E, et al., 1999[17]	76 Nondialyzed (37 DM/ 39 non-DM)	Japan	16.9 ± 9.4 (Total group) 22.3 ± 9.4 (Non-DM) 11.4 ± 5.6 (DM)	NA	(+) Albumin, (–)DM, (–) serum phosphate, (+) $1,25(OH)_2D$
Gonzalez EA, et al., 2004[18]	43 Nondialyzed 103 HD patients	USA	18.5 ± 11.2 (Nondialyzed) 10.7 ± 6.8 (HD)	86% Nondialyzed 97% Hemodialysis	(–) PTH, (+) $1,25(OH)_2D$
Laclair RE, et al., 2005[19]	201 Nondialyzed (CKD stages 3 and 4)	USA	19.4 ± 13.6 (Total group) 23.3 ± 14.5 (CKD stage 3) 18.6 ± 13.3 (CKD stage 4)	71% CKD stage 3 84% CKD stage 4	(+) Serum calcium, (–) PTH, (+) $1,25(OH)_2D$ and sex
Cuppari L, et al., 2008[16]	144 Nondialyzed nondiabetic CKD patients	Brazil	34.3 ± 18.3	40%	(+) Serum calcium, (–) proteinuria, (+) $1,25(OH)_2D$
Wolf M, et al., 2007[20]	825 Incident HD patients	USA	21.0 ±13.0	78%	(–) PTH, (+) albumin, (+) serum calcium, (+) $1,25(OH)_2D$
Saab G, et al., 2007[21]	131 Hemodialysis patients	USA	16.7 ± 8.3	92%	No association was found.
Taskapan H, et al., 2006[22]	273 Peritoneal dialysis patients	Greece/ Turkey	7.3 ± 8.4 (Total group) 8.1 ± 9.2 (Non-DM) 4.8 ± 4.1 (DM)	96%	(–) Age, (+)DM, (+) serum calcium, (+) $1,25(OH)_2D$
Ewers B, et al., 2008[23]	173 Kidney transplant patients	Denmark	21.6 (15.6–31.2)* (Women) 18.2 (12.0–26.8)* (Men)	81%	(–) Smoking, (+) age, (–) sun avoidance, (–) BMI, (+) use of vitamin D supplements, (+) albumin

Cuppari L. J Ren Nutrition 2009; 19: 38-43.

Is hypovitaminosis D discussed in our clinical guidelines?

NF/KDOQI guidelines

- **CKD stages 3 & 4 (opinion)**
  - Active vitamin D sterol (calcitriol, alfacalcidol, or doxercalciferol)
    - If serum levels of 25(OH)-vitamin D ≥ 75 nmol/L & plasma levels of intact PTH > target range
  - Vitamin D2 (ergocalciferol)
    - If serum levels of 25(OH)-vitamin D < 75 nmol/L & plasma levels of intact PTH > target range
- **CKD stage 5 and/or HD/PD (opinion)**
  - Active vitamin D sterol
    - When serum levels of intact PTH levels >33.0 pmol/L

Am J Kid Dis 2003; 42 (4Supp3): S84-9.

KDIGO guidelines

- In patients with CKD stages 3–5D, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions (2C).

- We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (2C).
  - Weak recommendations with low quality of evidence

KI 2009; 76 (Supp113): S22-49.

Where can vitamin D be found?

Source of vitamin D

- **Natural Sources**
  - Exposure to sun light
  - Salmon, sardines, mackerel, tuna, cod liver oil, eggs yolk
- **Fortified foods**
  - Milk, orange juice, margarine, infant preparation

Holick MF. NEJM 2007;357: 266-81.

Source of vitamin D

- **Inactive vitamin D sterols**
  - Ergocalciferol → vitamin D2 (**MVI**, Drisdol®, Osteoforte®)
  - Cholecalciferol → vitamin D3 (Cal-Mag, cod liver oil, MVI, "vitamin D products")
    - Cholecalciferol about 2 times more potent

  } Require liver and kidney activation

- **Vitamin D receptor activators (VDRAs)**
  - **Partially active vitamin D sterols**
    - Calcifediol (25-hydroxyvitamin D3)
      - Not available in Canada
    - Alfacalcidol (1α-hydroxyvitamin D3)
    - Doxercalciferol (1α-hydroxyvitamin D2)

  } Requires kidney activation

  } Require liver activation

  - **Active vitamin D sterols**
    - Calcitriol (1α,25-dihydroxyvitamin D3)
    - Paricalcitol (19-nor-1α,25-dihydroxyvitamin D3)
      - Not available in Canada
    - Maxicalcitol (22-oxacalcitriol)
      - Not available in Canada

Vitamin D– Appropriate dose as per NF/KDOQI guidelines

- **CKD stages 3 & 4 (opinion)**

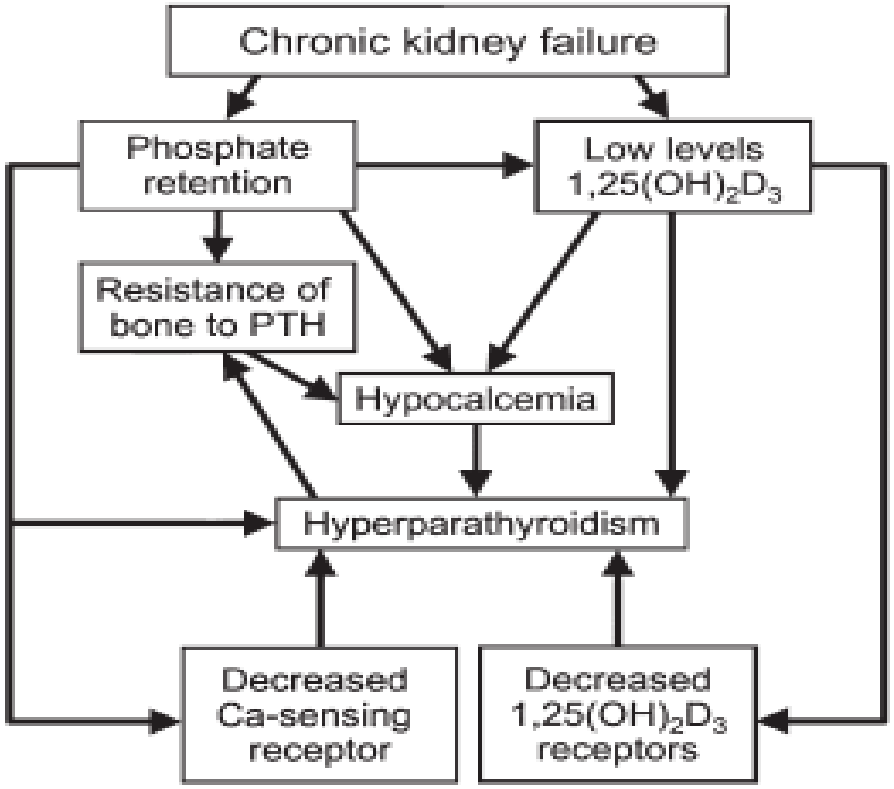
Table 26. Recommended Supplementation for Vitamin D Deficiency/Insufficiency in Patients with CKD Stages 3 and 4

Serum 25(OH)D (ng/mL) [nmol/L]	Definition	Ergocalciferol Dose (Vitamin D_2)	Duration (months)	Comment
<5 [12]	Severe vitamin D deficiency	50,000 IU/wk orally x 12 wks; then monthly	6 months	Measure 25(OH)D levels after 6 months
		500,000 IU as single I.M. dose		Assure patient adherence; measure 25(OH)D at 6 months
5-15 [12-37]	Mild vitamin D deficiency	50,000 IU/wk x 4 weeks, then 50,000 IU/month orally	6 months	Measure 25(OH)D levels after 6 months
16-30 [40-75]	Vitamin D insufficiency	50,000 IU/month orally	6 months	

Am J Kid Dis 2003; 42 (4Supp3): S84-9.

In patients with renal failure, what is the evidence that vitamin D supplements will improve bone health?

Secondary HPT and vitamin D



Hudson JQ. Ann Pharmacother 2006; 40:1584-93

Vitamin D treatment

- **Expected effect**
  - Prevents parathyroid gland hyperplasia
  - Suppresses PTH synthesis
  - Stimulates vitamin D receptors (VDR) in parathyroid cells
  - ↑ Ca^{2+} & PO_4^{2-} absorption
  - Maintains normal bone formation
  - ↑ bone mineral density (BMD)

Hudson JQ. Ann Pharmacother 2006; 40:1584-93

Vitamin D treatment

- **Concerns**
  - Vascular & soft tissue calcification
    - ↑ morbidity & mortality
  - Hypercalcemia
  - Hyperphosphatemia
  - Oversuppression of PTH
    - Induction of adynamic bone disease

Hudson JQ. Ann Pharmacother 2006; 40:1584-93

Vitamin D in CKD pre-dialysis

Reference	Study Design	Vit D therapy	Main results
Deville et al., 2006	Observational, CKD 3-5, n=85pts	Ergo. 800-100,000 IU/wk (median f-u 3 months)	↑25(OH)D (43.5-105.3nmol/L) ↓iPTH only in CKD stage 4 (20.1 to 16.5 pmol/L, p<0.05)
Zisman et al. 2007	Observational, CKD 3-4, n= 52	Ergo. as per K/DOQI (follow-up < 6 months)	↑25(OH)D > 75 nmol/L in 60% of patients ↓iPTH only in CKD stage 3 (13.1%, p=0.041)
Al-Aly et al., 2007	Restrospective, CKD3-4, n=66	Ergo. 50,000 IU Qweek x 3 months, then Qmonth x 6 ms	↑25(OH)D (41.5 ± 1.75 to 68 ± 4.5 nmol/L) ↓iPTH only in CKD stage 3 (24.3 to 20.3 pmol/L, p<0.05)
Chandra et al., 2008	DB RCT CKD stage 3-4, n=20	Chole. 50,000 IU Qweek x 3 months	↑25(OH)D (43.3 to 123.5 nmol/L) No change in iPTH

RCT cholecalciferol in CKD

Dogan E. *Renal failure* 2008: 30:407-10.

Objective	To determine the effect of cholecalciferol treatment on BMD parameters in patients with stage 3.
Design	Un-blinded RCT
Setting	Community hospital CKD clinic
Inclusion	Stage 3 CKD not taking vitamin D or phosphorus binder
Exclusion	Proteinuria > 5g/d; poorly controlled DM, HTN or vasculitis, iPTH < 22 pmol/L, Ca > 2.63 mmol/L, PO_4 > 2.1 mmol/L
Follow-up	1 month

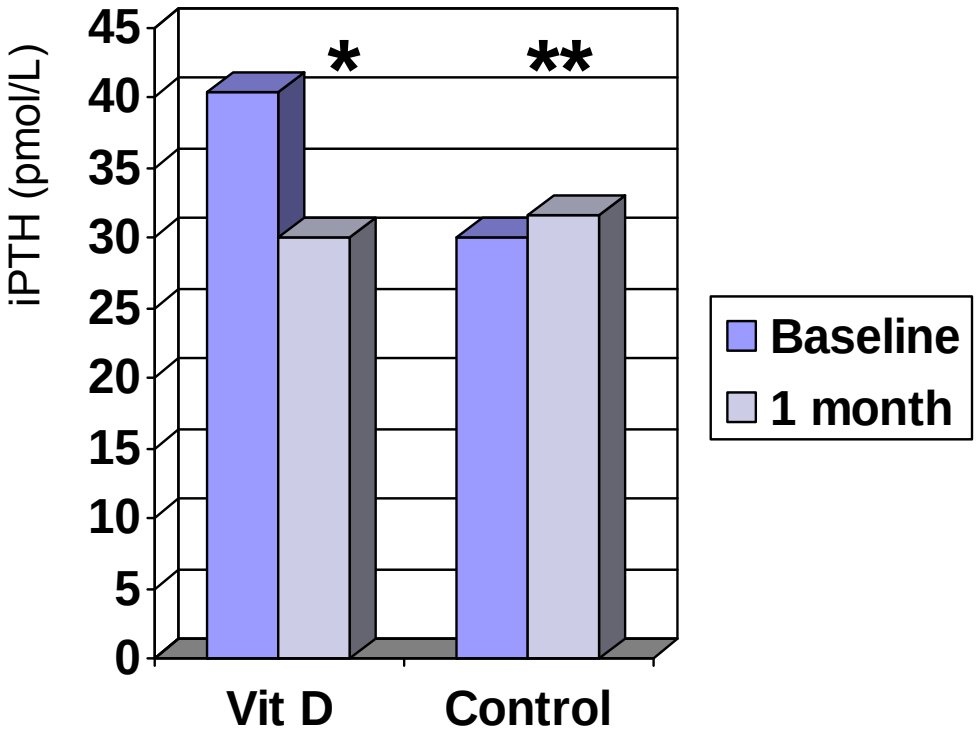
RCT cholecalciferol in CKD

Dogan E. *Renal failure* 2008: 30:407-10.

Intervention	- Same dosing regimen regardless of initial serum 25(OH)D level → Cholecalciferol, 300,000 IU PO x once **vs.** no vitamin D supplement
Outcomes	iPTH, Ca, PO_4, alk phos, sCr, BUN (baseline & follow-up), BP, microalbiminuria
N	40 patients randomized - 50% were male; mean age: 49 ± 14 years old

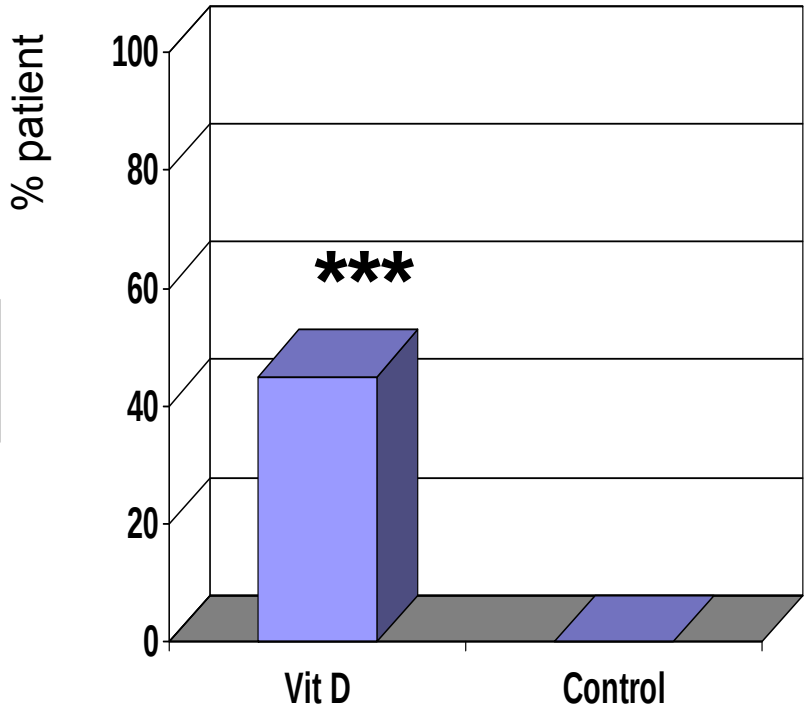
RCT cholecalciferol in CKD

Dogan E. *Renal failure* 2008: 30:407-10.



* p<0.001

** p= 0.04



% of patient showing a 30% decrease iPTH results at 1 month

*** p< 0.001

RCT cholecalciferol vs. Doxercalciferol in CKD

Moe SM. *Clin J Am Soc Nephrol* 2010

Objective	To determine the effect of cholecalciferol vs. doxercalciferol on BMD parameters in 25(OH)D insufficient patients with CKD stage 3 and 4.
Design	Single blinded randomized trial (pilot study)
Setting	Community hospital CKD clinic
Inclusion	Stage 3-4 CKD, iPTH higher than K/DOQI recommendations, calcidiol <50 nmol/L
Exclusion	iPTH > 40 pmol/L, Ca > 2.4 mmol/L, PO_4 > 1.6 mmol/L poorly controlled HTN, liver disease, cirrhosis, malbsorption, chronic diarrhea, excepted to required dialysis < 6 months, use of calcimimetic or vitamin D (except MVI) 30 days before enrollment
Follow-up	3 months

RCT cholecalciferol vs. Doxercalciferol in CKD

Moe SM. *Clin J Am Soc Nephrol* 2010

Intervention	- Same dosing regimen regardless of initial serum 25(OH)D level → Cholecalciferol, 4,000 IU PO OD x 1 month, then 2,000 IU PO OD x 2 months **vs.** Doxercalciferol, 1 mcg PO OD
Outcomes	iPTH, 25(OH)D, Ca, PO_4, alk phos, sCr, BUN (baseline & follow-up)
N	55 pts randomized, 47 pts had more than 1 follow-up visit - ↑ eGFR in doxercalciferol group (36.4 ± 10.7 vs 29.6 ± 7.4 ml/min, p=0.02)

RCT cholecalciferol vs. Doxercalciferol in CKD

Moe SM. *Clin J Am Soc Nephrol* 2010

Endpoints	Cholecalciferol			Doxercalciferol			Between Tx group p
	Baseline	Final	Pre-post p	Baseline	Final	Pre-post p	
25(OH)D (nmol/L)	35.0± 15.3	93.0± 25.3	**<0.001**	37.5± 13.8	35.0± 15.3	<0.59	**<0.001**
iPTH (pmol/L)	10.9± 4.3	9.7± 4.9	0.15	10.6 ±4.4	8.0 ±4.9	**0.006**	0.19

Vitamin D in CKD dialysis

Reference	Study Design	Vit D therapy	Main results
Saab et al., 2007	Retrospective, n=119 HD pts	Ergo. 50,000 IU Qmonth x 6months	↑25(OH)D (42.3 ± 21.3 to 133.8 ± 40.8 nmol/L) No change in iPTH
Blair D et al., 2008	Retrospective, n=344 HD pts	Ergo. 50,000 IU Qweek x 6 months	↑25(OH)D (46.0 ± 22.5 to 105 ± 61.8 nmol/L) No change in iPTH
Shah et al., 2005	Observational, n=29 PD pts	Ergo. 50,000 IU Qweek x 1 month	↑25(OH)D (median from 17.5 to 75 nmol/L) No change in iPTH
Tokmak et al., 2008	Prospective, n=64 HD pts	Chole. 20,000 IU Qweek x 9months	↑25(OH)D (41.6 ± 24 to 199.2 ± 67.9 nmol/L) No change in iPTH
Bouchard et al., 2008	Prospective, n=27 PD pts	Ergo. 41,440 IU Qweek x 1 month	↑25(OH)D (30.0 ± 9.5 to 42.7 ± 13.0 nmol/L) No change in iPTH

In patients with renal failure, what are the evidence that vitamin D supplements have non-traditional beneficial effects ?

Vitamin D nontraditional functions

- VDRs situated in brain, heart, stomach, pancreas, skin, breast, gonads, T and B lymphocytes and monocytes
- Vitamin D deficiency associated in general population with:
  - ↑ risk of prostate, breast, colorectal cancers
  - ↑ risk of autoimmune diseases (MS, rheumatoid arthritis, type I DM)
  - ↓ insulin production
  - ↓ cognitive performance
  - ↑ renin production
  - ↑ risk of heart failure (↓ cardiomyocyte remodeling and ↑inflammation)
  - ↑ risk of tuberculosis, pneumonia, gingivitis

Holick MF. Seminar in Dialysis 2005; 18(4): 266-75.

Coen G. J Nephrol 2008; 21:313-323.

Vitamin D nontraditional roles in CKD

- Pre-dialysis patients
  - 25(OH)D level is an inverse predictor of disease progression and mortality in CKD stage 3-5
    - Ravani P. Kidney Int 2009; 75: 88-95.
    - Mehrotra R. Kidney Int 2009; 76: 977-83.
- Dialysis patients
  - Incident HD patients may have ↑ 90 days mortality risk if 25(OH)D < 75 nmol/L
    - Wolf M. *Kidney Int* 2007; 72: 1004-13.
  - 25(OH)D is an inverse predictor of cardiovascular outcomes in PD pts.
    - Wang AYM. Am J Clin Nutr 2008; 87:1631-8.
- No data on impact of treatment with cholecalciferol/ergocalciferol on clinical outcomes

Nontraditional effects of vitD_2

- Dialysis patients
  - Blair D et al. *J Ren Nutr 2008; 18: 375-82.*
    - Retrospective study, ergocalciferol, 50,000 IU Qweek x 6 months (n = 344 HD pts)
    - Improvement in HbA1c from 6.9 ± 1.9% to 6.4 ± 1.5% (p<0.0005)
    - Improvement in Hgb level from 121 ± 16 g/L to 123 ± 14 g/L (p<0.0005)
  - Saab G et al. *Nephron Clin Pract* 2007; 105: c132-8.
    - Retrospective study, ergocalciferol, 50,000 IU Qmonth x 6 months (n=119 HD pts)

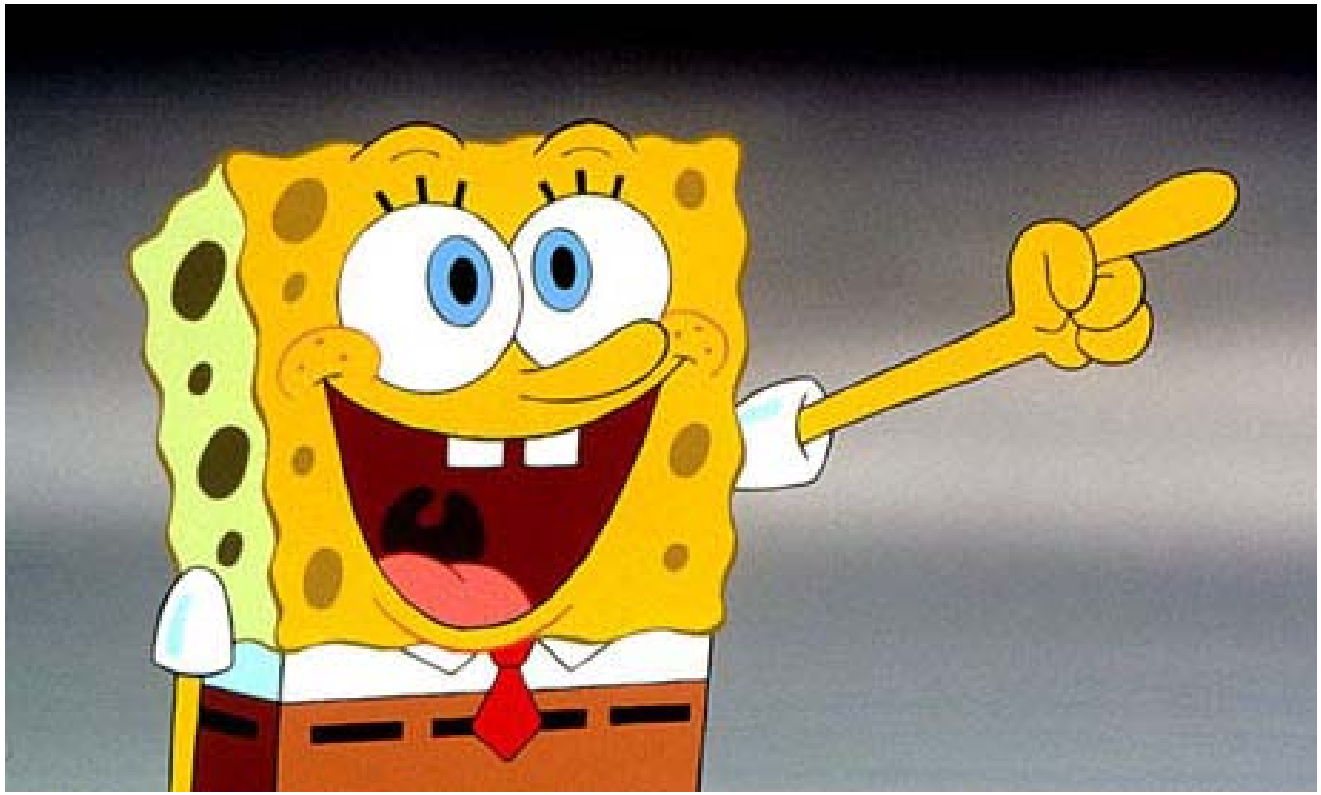
Table 3. Epoetin dosing

	Epoetin dose, U/week – April 2005			Epoetin dose, U/week – October 2005		
	median	25%	75%	median	25%	75%
All patients	11,700	5,775	24,000	9,000*	3,900	18,300
Baseline 25(OH)D <20	14,400	6,000	27,000	9,600**	4,875	20,400
Baseline 25(OH)D ≥20	7,200	5,400	23,700	5,400	2,700	15,000

* p = 0.001 and ** p = 0.003 vs. April dose.

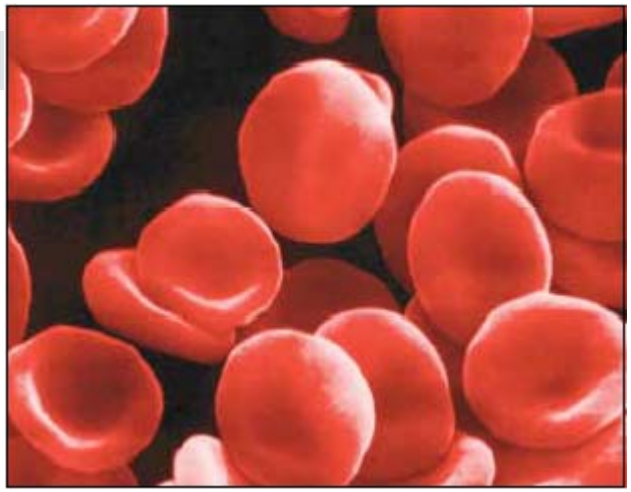
  - Shah et al. *Perit Dial Int 2005; 25:362-6.*
    - Prospective study, ergocalciferol, 50,000 IU Qweek x 1 month (n=23 PD pts)
    - Improvement in muscle weakness (p<0.002) and bone pain scores (p=0.03)

How we ready to wrap up???



Lets go back in time…

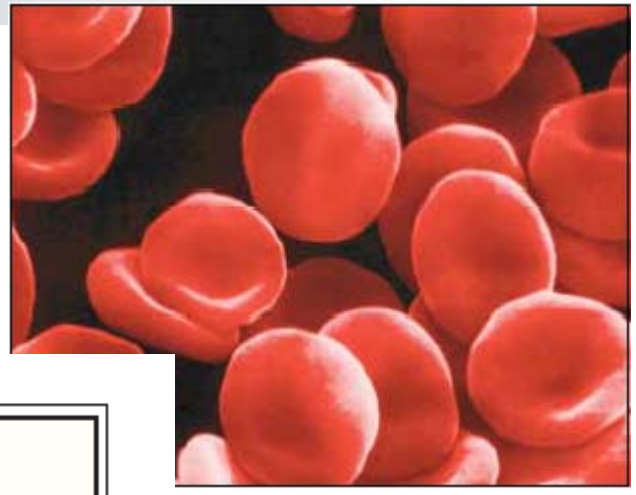
The ESA debate…



- ESA therapy⇒ replacement of a deficient hormone in CKD patient
- Observational studies suggesting anemia:
  - ↓ QOL
  - ↓ energy and exercise capacity
  - ↓ neurocognitive function
  - ↑ mortality
  - ↑ LVH rate
  - ↑ progression of renal failure

⇒ **Normalizing Hgb level could be desirable in CKD patients**

The ESA debate…



The NEW ENGLAND JOURNAL of MEDICINE

Nephrol Dial Transplant (2007) 22: 309–312
doi:10.1093/ndt/gfl824

NDT

EDITORIAL

No TREATment with Darbepoetin Dosed to Hemoglobin 13 Grams per Deciliter in Type 2 Diabetes with Pre-Dialysis Chronic Kidney Disease – Safety Warnings for Erythropoiesis-Stimulating Agents

Frederic R. Curtiss, PhD, RPh, CEBS, and Kathleen A. Fairman, MA

Meta-analysis: Vitamin D in CKD

Ann Intern Med 2007; 147: 840-53.

Table 2. Summary of Trial Results for Patient-Level End Points for Vitamin D Treatment in People with Chronic Kidney Disease

Outcome Analyzed (Reference)	Studies Reporting Outcome, *n*	Patients Enrolled, *n*	Relative Risk (95% CI)*	Heterogeneity (Chi-Square)	I^2, %†
Established vitamin D sterol vs. placebo or no treatment					
Fracture (12, 47, 49)	3	103	1.00 (0.06 to 15.41)	–	–
Parathyroidectomy (11, 47)	2	133	0.82 (0.05 to 12.47)	2.79	64.1
Development of bone pain (42)	1	74	0.41 (0.02 to 9.25)	–	–
Newer vitamin D vs. placebo or no treatment					
Development of bone pain (59)	1	35	0.20 (0.01 to 4.65)	–	–

Meta-analysis: Vitamin D in CKD

Ann Intern Med 2007; 147: 840-53.

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Outcome Analyzed (Reference)	Studies Reporting Outcome, *n*	Patients Enrolled, *n*	Relative Risk (95% CI)*	Heterogeneity (Chi-Square)	I^2, %†
Established vitamin D sterol vs. placebo or no treatment					
All-cause mortality (11, 14, 54)	3	259	1.34 (0.42 to 4.26)	1.77	0
Newer vitamin D vs. placebo or no treatment					
All-cause mortality (24, 41)	2	250	2.40 (0.36 to 16.01)	0.03	0
Vitamin D vs. calcium					
All-cause mortality (34)	1	47	5.21(0.26 to 102.98)	–	–
Intravenous vs. oral vitamin D					
All-cause mortality (86)	1	28	0.33 (0.01 to 7.55)	–	–

Cochrane database 2009

THE COCHRANE COLLABORATION®

Vitamin D compounds for people with chronic kidney disease not requiring dialysis (Review)

Authors' conclusions

There are not sufficient data to determine the effect of vitamin D compounds on mortality and cardiovascular outcomes in people with CKD not requiring dialysis. While vitamin D compounds reduce serum PTH (49.3 pg/mL (5.6 pmol/L)) compared with placebo, the relative clinical benefits of PTH lowering versus treatment-related increases in serum phosphorus and calcium remain to be understood.

Cochrane database 2009

THE COCHRANE COLLABORATION®

Vitamin D compounds for people with chronic kidney disease requiring dialysis (Review)

Authors' conclusions

We confirm that vitamin D compounds suppress PTH in people with CKD and requiring dialysis although treatment is associated with clinical elevations in serum phosphorus and calcium. All studies were inadequately powered to assess the effect of vitamin D on clinical outcomes and until such studies are conducted the relative importance of changes in serum PTH, phosphorus and calcium resulting from vitamin D therapy remain unknown. Observational data showing vitamin D compounds may be associated with improved survival in CKD need to be confirmed or refuted in specifically designed RCTs.

Vitamin D in CKD

- **My conclusion**
  - Hypovitaminosis D is common in CKD population
  - Scarcity of data to support vitamin D use
    - Probably a safe option
    - Efficacy? Pill burden? Cost? Monitoring?
  - Observational studies supporting use of vitamin D
  - Poor trials quality
    - Small, short duration trials, not intended to evaluate clinical outcomes
  - Heterogeneity in results between trials

Vitamin D in CKD

- **In clinical practice**
  - For sHPTin CKD stage 3 & 4 only,
    - Cholecalciferol, 1,000- 1,200 IU every day
    - Ergocalciferol, 50,000 IU Qweek x 3 months, then 50,000 IU Qmonth
  - For sHPT, use of active vitamin D in CKD stage 5, dialysis patients, or patients failing cholecalciferol
  - We are not stopping, but not encouraging use of cholecalciferol/ergocalciferol in CKD patients
  - Other considerations:
    - Cost of treatment
    - Cost of 25(OH)D levels
  - **I'm taking vitamin D every day!!!!**

Stay tuned…

- Over 20 active studies
  - DIVINE study
    - Ergocalciferol vs. pb on risk of infection in ESRD
  - D2D study
    - Ergocalciferol vs. pb on muscle weakness, fracture and bone pain in dialysis pts
  - POSH-D
    - Cholecalciferol vs. pb on prevention of sHPT in CKD pts stage 2-3
  - Impact of ergocalciferol vs. paricalcitol on iPTH in CKD stage 3-4
  - Impact of ergocalciferol vs. pb on proteinuria in CKD stage 3-4

http://www.clinicaltrials.gov

Back to the case...

The end!

Cost to consider…

- 25OHD level
  - 95$/test (BC BioMed)
- Vitamin D supplements
  - Ergocalciferol, 50,000 IU/week
    - Drisdol® ⇒ 2.34$/week
    - Osteoforte⇒ 0.21$/week
  - Cholecalciferol, 50,000 IU/week
    - Generic ⇒ 3.50$/week

BMD and cardiovascular disease

- For every 33 pmol/L ↑ in iPTH,compared to 16-33 pmol/L, ↑ in CV mortality by 10-20%
- For every 0.16 mmol/L ↑ in HPO4, compared to 1.62 to 1.78 mmol/L, ↑ in CV mortality by 10-20%
- For every 0.16 mmol/L ↑ in Ca, compared to 2.25 to 2.38 mmol/L, ↑ in CV mortality by 10-20%

Treatment

- Vitamin D deficiency
  - Goals: vitamin 25 (OH) D level: 30-40 ng/mL
  - Vitamin D2, 50,000 IU PO weekly x 8 weeks, then 50,000 IU twice monthly
  - Vitamin D3, 1,000 IU PO once daily
  - Exposure to sunlight or bed tanning!!!

Holick MF. Seminar in Dialysis 2005; 18(4): 266-75.

KDIGO Guidelines draft

- Only measure 25(OH)vitD if ↓ Ca; ↑ iPTH, clinical symptoms
- Ergocalciferol in stage 3-4 CKD and active vitamin D for stage 5 CKD

Vitamin D assay

- 25(OH)vitD or calcidiol has a longer $t_{1/2}$ of 3 weeks and take into account multiple sources of vitamin D
- Vitamin D assay not standardized and definition of deficiency not validated
- Benefit of replacing vitamin D unproven$\Rightarrow$ questionable value of measuring vitamin D level
- Calcitriol has of $t_{1/2of}$ 6 hours and levels altered by exogenous calcitriol or other vitamin D analogous

FGF-23 and klotho

- FGF-23 is a counter-regulatory hormone for vitamin D, induces renal phosphate wasting and negative regulator of PTH expression
- FGF-23 is secreted mainly by osteocytes
- C terminal and intact FGF-23
  - Link to doubling of sCR
  - Mortality in hemodialysis patients

Vitamin D– Appropriate dose

- **Study by Tokmak et al.**
  - Prospective study including 64 HD patients
  - Cholecalciferol, 20 000 IU/week x 9 months

	June 2004 (n=64)	Feb 2005 (n=65)
25(OH)D < 37.5 nmol/L	95% (61)	8% (4)
25(OH)D 37,5-75 nmol/L	5% (3)	34% (20)
25(OH)D > 75 nmol/L	0% (0)	57% (31)

Nephrol Dial Transplant 2008; 23: 4016-20.