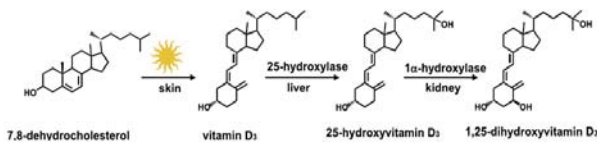


Vitamin D Deficiency and Supplement in CKD Patients

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황 현 석

Vitamin D Synthesis



Dusso A et al. Best Pract Res Clin Endocrinol Metab. 2011;25:647

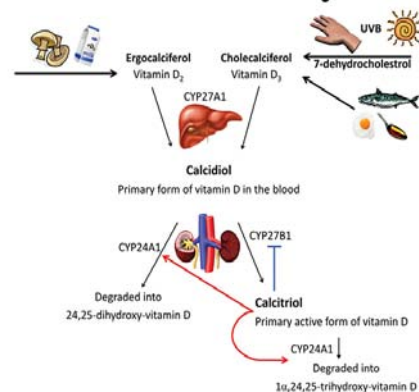
Nutritional VitD

- Lack both 1(OH) and 25(OH)
- Supplemented by oral intake
- VitD₂
 - From plants
 - Ergocalciferol
 - Not biologically active
- VitD₃
 - Made in the skin or ingested from animal food
 - Cholecalciferol
 - Not biologically active

VitD Activation Process

- 25(OH)D
 - Known as Calcidiol
 - Pro-hormone
 - Storage form, not biologically Active
- 1,25(OH)₂D
 - Known as Calcitriol
 - Real hormone
 - Biologically active

VitD Pathway



Synthetic Vitamin D Sterols (VitD Receptor Activator)

Vitamin D prohormones	
1- α -(OH) D ₃	Alfacalcidol
1- α -(OH) D ₂	Doxercalciferol
Active vitamin D sterols	
1- α -25-(OH) ₂ D ₃	Calcitriol
22-oxa-1, 25(OH) ₂ D ₃	Maxacalcitol
1,25(OH) ₂ -26, 27-F ₆ -D ₃	Falecalcitriol
19-Nor-1, 25(OH) ₂ D ₂	Paricalcitol

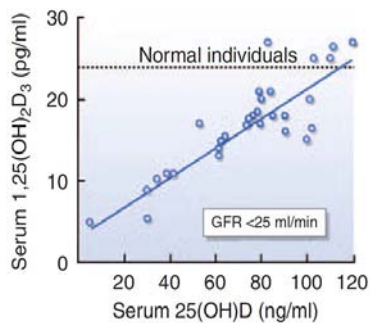
Al-Badr W et al. Clin J Am Soc Nephrol. 2008;3:155

VitD Deficiency Marker: 25(OH)D vs. 25(OH)₂D

	25(OH)D	25(OH) ₂ D
Half life	3 weeks	4hrs
Biologic significance	Storage form	Active biologic action
Clinical correlation	Good	Normal level in fracture and rickets
Medication effect on value	Rare	Frequently affected by active VitD

Zidehsrai MP et al. Nephrology. 2009;14:374

Strong Correlation in CKD: 25(OH)D vs. 1,25(OH)₂D

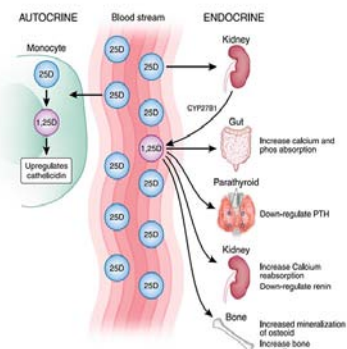


Dusso AS et al. Kidney Int. 2011;79:715

Assay of 25(OH)D

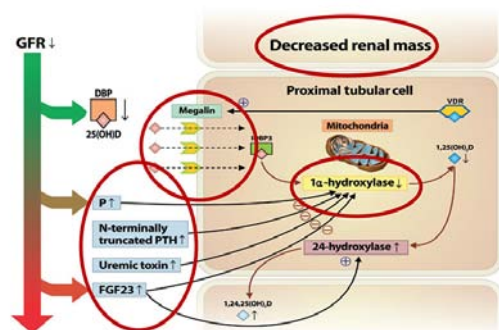
- Competitive protein binding assay
- HPLC
 - Requires expertise and special instrument, expensive
 - Differentiate 25(OH)D₂ and 25(OH)D₃
- RIA
 - Not automatic
- Chemiluminescence assay
 - Automatic, sum of 25(OH)D₂ and 25(OH)D₃

Two Activation Process of Vitamin D



Melamed ML et al. Clin J Am Soc Nephrol. 2012;7:358

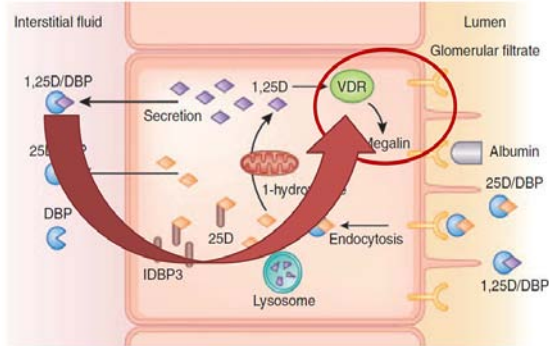
Altered Vitamin D Metabolism in CKD



Kim CS et al. Korean J Intern Med. 2014;29:416

Rate-limiting Step in 25-hydroxyvitamin D Delivery

Megalyn is induced by 1,25-dihydroxyvitamin D



Dusso AS et al. *Kidney Int.* 2011;79:715

Effect of FGF-23 on VitD Level Reduction

- Direct inhibition of 1 α -hydroxylase
- Induces the expression of 24-hydroxylase, the enzyme responsible for the degradation of 1,25-dihydroxyvitamin D

Criteria of VitD Deficiency

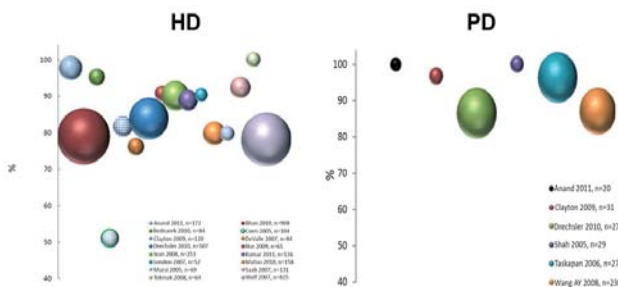
25 (OH) Vitamin D Concentrations	Vitamin D Status
0-10 ng/ml	Deficient
10-30 ng/ml	Insufficient
30-150 ng/ml	Sufficient
>150 ng/ml	Potentially Toxic
The reference interval for 1, 25 (OH)2 vitamin D is 25-66 pg/ml.	

High Prevalence of VitD Deficiency in CKD Patients: US

	CKD Stage 3	CKD Stage 4
No. of patients	65	113
Calcidiol sufficient (>30 ng/mL) (%)	29	17
Calcidiol insufficient (10-30 ng/mL) (%)	57	58
Calcidiol deficient (<10 ng/mL) (%)	14	26
Total (%)	61	84

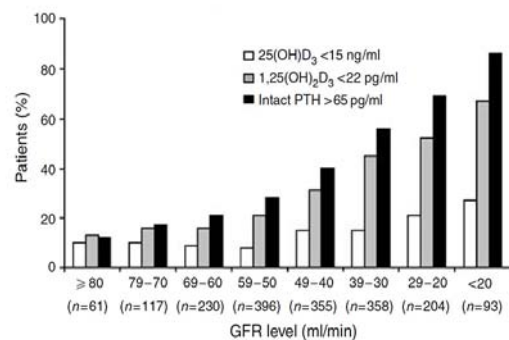
LaClair RE et al. *Am J Kidney Dis.* 2005;45:1026

High Prevalence of VitD Deficiency in Dialysis Patients



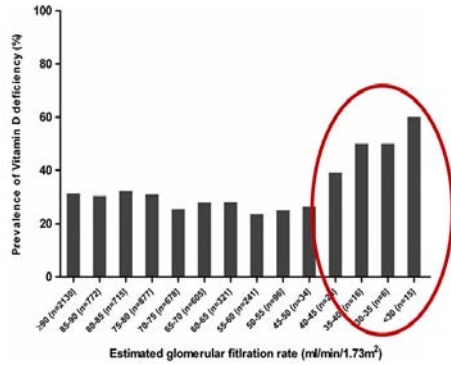
Singer RF et al. *Semin Dial.* 2013;26:40

Prevalence of VitD Deficiency Increases, as eGFR Decreased



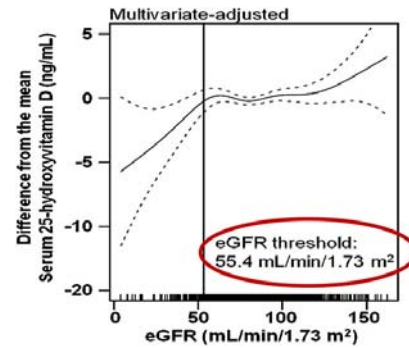
Levin A et al. *Kidney Int.* 2007;71:31

Prevalence of VitD Deficiency: Korean



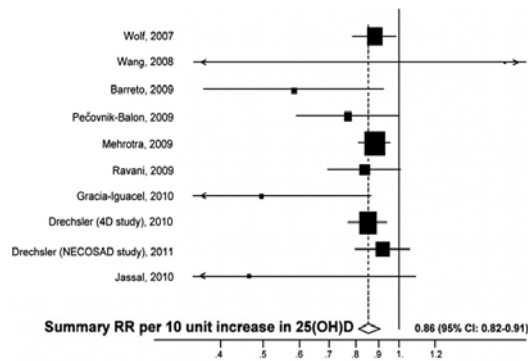
Oh YJ et al. Nephrol Dial Transplant. 2012;27:2396

eGFR Threshold to Predict 25(OH)D Deficiency in Korean



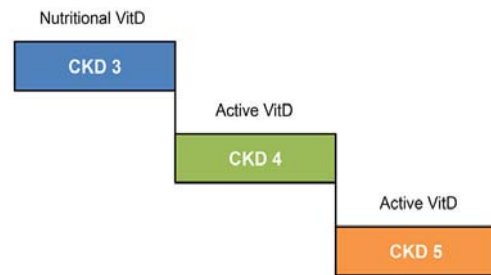
Oh YJ et al. Nephrol Dial Transplant. 2012;27:2396

VitD Status and Mortality Risk in CKD



Pilz S et al. Am J Kidney Dis. 2011;58:374

Step-wise Approach to VitD Deficiency (KDOQI Guideline)



Methods to Treat VitD Deficiency

CKD stage	Preventive and maintenance measures to avoid deficiency	Treatment of Deficiency
CKD 2 and 3	Control serum phosphate, 1000 IU vitamin D ₃ /day, 50,000 IU vitamin D ₂ /2 wks, maintenance dose is 50,000 vitamin D ₂ /2 or 4 wks	50,000 IU vitamin D ₂ once/wk for 8 wk; repeat for another 8 wk, if 25(OH)D <30 ng/ml
CKD 4 and 5	1000 IU of vitamin D ₃ /day, 50,000 IU of vitamin D ₂ /2 wks, Need to treat with 1,25(OH) ₂ D ₃ or active analogue	0.25–1.0 µg calcitriol by mouth twice a day 1–2 µg paricalcitol IV/3 days 2–4 µg paricalcitol by mouth three times/ wk, 10–20 µg doxercalciferol by mouth three times/wk

Holick MF et al. N Engl J Med. 2007;357:266

KDOQI Guideline

In CKD Stages 2-4:

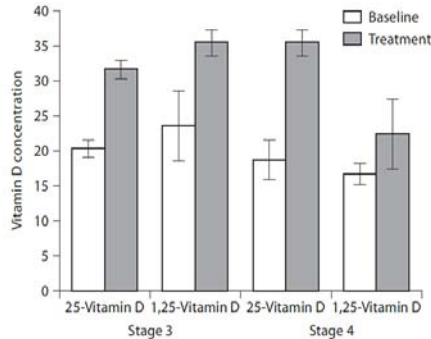
- 8.1 If serum PTH is above the target range for the stage of CKD (Table 3, Guideline 1) serum 25-hydroxyvitamin D should be measured. (EVIDENCE) Periodic assessment is warranted thereafter if dietary or lifestyle changes have occurred in the patient. (OPINION)
- 8.2 If the serum level of 25-hydroxyvitamin D is <30 ng/mL, supplementation with vitamin D₂ (ergocalciferol) should be initiated (see Table 15). (OPINION)

In CKD Stage 5:

- 8.4 Therapy with an active vitamin D sterol (calcitriol) should be provided if the serum levels of PTH are >300 pg/mL. (OPINION) See Guideline 9.

Noordzij M et al. Am J Kidney Dis. 2005;46:925

Ergocalciferol (Nutritional VitD₂) Effect in CKD 3 and 4



Zisman AL et al. Am J Nephrol. 2007;27:36

Ergocalciferol (Nutritional VitD₂) in CKD 3 and 4

	Pretreatment	Posttreatment	P
CKD stage 3 (n = 44)			
25-Hydroxyvitamin D (ng/mL)	17.5 ± 0.8	27.6 ± 1.7	<0.005
Plasma intact PTH (pg/mL)	174 ± 21	136 ± 12	<0.005
CKD stage 4 (n = 22)			
25-Hydroxyvitamin D (ng/mL)	14.7 ± 1.3	26.4 ± 4.5	<0.005
Plasma intact PTH (pg/mL)	345 ± 58	306 ± 65	0.195

Al-Aly Z K et al. Am J Kidney Dis. 2007;50:59

Cholecalciferol (Nutritional VitD₃) in CKD 3 and 4

Table 2
Serum Measures of Vitamin D Status and Bone Metabolism in Patients With Chronic Kidney Disease
Treated With Placebo or Cholecalciferol (Vitamin D₃)^{a,b}

Analyte	Placebo			Cholecalciferol		
	Week 0	Week 6	Week 12	Week 0	Week 6	Week 12
Total calcium, mg/dL	9.0 (8.8-9.3) n = 9	...	9.5 (9.3-9.6) n = 10	9.1 (8.9-9.4) n = 9	...	9.7 (9.5-9.8) n = 10
25(OH)D, ng/mL	18.6 (12.8-27.1) n = 10	21 (15.7-28.2) n = 9	19.5 (13.4-28.4) n = 10	17.3 (11.8-25.2) n = 10	44.5 (33.1-59.8) n = 7	49.4 (33.9-72.0) n = 10
PTH, pg/mL	290.5 (179.7-469.8) n = 10	335.1 (214.2-524.1) n = 9	269.7 (153.3-474.5) n = 10	288.9 (178.7-467.2) n = 10	254.7 (161.4-401.9) n = 7	200.5 (114.0-352.8) n = 10

Chandra P et al. Endocr Pract. 2008;14:10

Nutritional VitD Effects in Dialysis Patients

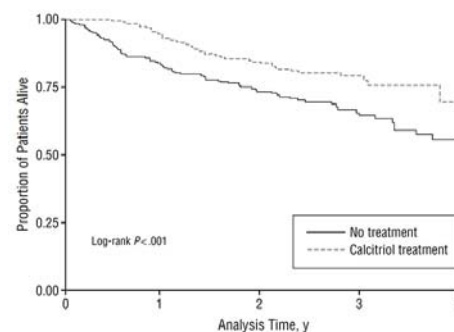
Author /year	N	Regimen	Serum VitD Level change	PTH Change
Shah et al. 2005	29 PD patients	Ergocalciferol 50,000 IU/wk for 4 wk	<7 to 30 ng/ml	No change in PTH
Saab et al. 2007	119 HD patients	Ergocalciferol 50,000 IU/mo for 6 mo	17 to 54 ng/ml	No change in PTH
Blair et al. 2008	344 HD patients	Ergocalciferol 50,000 IU/wk for 24 wk	18 to 42 ng/ml	No change in PTH
Jean et al. 2008	149 HD patients	Cholecalciferol 10 to 30 µg/day	30 to 126 nmol/L	13% of patients showed partial response
Jean et al. 2008	43 HD patients	Cholecalciferol 10 to 30 µg/day	28 to 118 nmol/l	PTH levels decreased

Kalantar-Zadeh K et al. Clin J Am Soc Nephrol. 2009;4:1529

Nutritional VitD₂ or D₃ in CKD

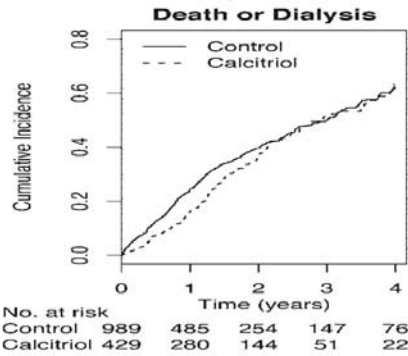
- Effective to increase the serum 25(OH) level
- Peripheral 1α-hydroxylase effect?
- Efficacy reducing the PTH level is greater in the early stage of CKD
- No data on clinical outcome (mortality and CVE)

Effects of Active VitD on Non-dialysis CKD



Kovesdy CP et al. Arch Intern Med. 2008;168(4):397

Effects of Active VitD on Non-dialysis CKD



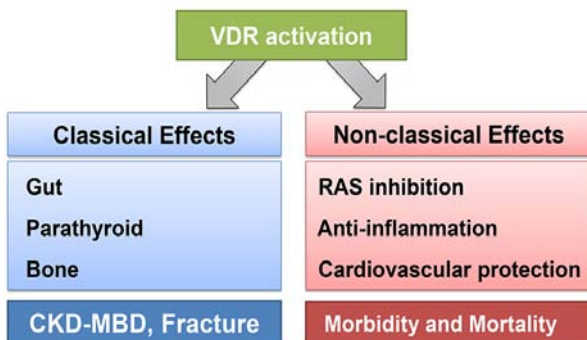
Shoben AB et al. *J Am Soc Nephrol.* 2008;19:1613

Effects of Active VitD on HD Patients

Author/year	N	Regimen	Results
Shoji et al., 2004	242	Oral alfacalcidol vs none	Lower cardiovascular mortality.
Teng et al., 2003	67,399	Paricalcitol vs. calcitriol	16% lower all-cause mortality with paricalcitol
Teng et al., 2005	51,037	Any VDRA vs. none	20% lower all-cause mortality
Melamed et al., 2006	1007	IV calcitriol vs. none	Lower all-cause mortality
Tentori et al., 2006	7731	Any VDRA vs. none	Lower mortality
Kalantar-Zadeh et al., 2006 and	58,058	Paricalcitol vs. none	Lower all-cause mortality
Lee et al., 2007			
Naves-Diaz et al., 2008	16,004	Oral calcitriol vs. none	Lower mortality with po calcitriol.
Shinaberger et al., 2008	34,307	Paricalcitol lower dose vs. higher dose	Higher paricalcitol dose associated with greater survival
Wolf et al., 2008	9303	VDRA vs. none	Mortality lower with VDRA treatment

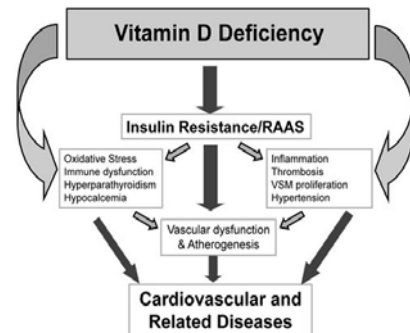
Kalantar-Zadeh K et al. *Clin J Am Soc Nephrol.* 2009;4:1529

Effects of VDR Activation



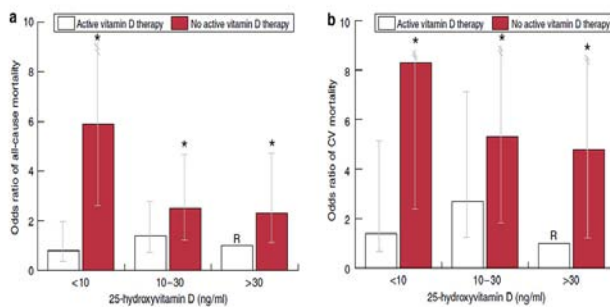
Cunningham J et al. *Kidney Int.* 2011; 79: 702

Conceptual model which vitamin D deficiency may lead to CVD



Artaza JN et al. *Clin J Am Soc Nephrol.* 2009;4:1515

Effect of VitD Replacement in HD Patients



Artaza JN et al. *Clin J Am Soc Nephrol.* 2009;4:1515