

To Treat or Not to Treat Vitamin D Deficiency

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Agenda

1. What's in a name?
2. What are normal Vit D levels? (You might be surprised)
3. What are the consequences of low Vit D?
4. Should everyone be tested for low vit D?
5. How should I treat low levels of vit D?
 - Which Rx?
 - How much?
 - What schedule?
 - How long?
 - Re-test?



Doctor, you said to take some vit
D but I can't figure out what to
buy or what any of the names
mean

Vitamin D Precursors

There are 2 parent forms of vit D called D2 and D3

D2 is an oral supplement derived from the plant sterol ergosterol and is a 28 carbon structure

D3 is synthesized in the skin after exposure to UV radiation of endogenous 7-dehydrocholesterol, a 27 carbon structure

D2 and D3 are actually “pro-vitamins” and both can be converted to biologically active vit D

Activation of Pro-Vitamin D2 and D3

Vit D2 and D3 have no biologic activity and must be modified by 2 hydroxylation reactions

Step 1 is addition of an OH group at carbon 25 and this happens in the liver to yield 25(OH)D

i.e. 25(OH)D₂ or 25(OH)D₃

Step 2 is addition of an OH group at carbon 1 and this occurs in the proximal tubules of the kidney to yield metabolically active 1-25(OH)₂D

i.e. 1-25(OH)₂D₂ or 1-25(OH)₂D₃

Note: 1-25(OH)₂D is also produced in many other tissues:
Pancreas, brain, lymph node, heart, gut, adrenals, prostate etc.

Vitamin D Terminology

The term Vit D is confusing because it may be used as a general term to refer to any of the forms of vit D

The pro-vitamin D2 is called ergocalciferol

The pro-vitamin D3 is called cholecalciferol

Sometimes, D2 and D3 are referred to as “Calciferal”

25(OH)D2 and 25(OH)D3 are called calcifediol

1-25(OH)₂D2 and 1-25(OH)₂D3, the active forms of vit D, are called calcitriol

Basic Physiology of Calcium, PTH, Vit D



↓Ca → ↑ PTH
↑PO₄ → ↑ PTH

↑ PTH → ↑ renal 1-hydroxylase → ↑1,25 vit D
↑ calcium resorption from bone and by kidney

↑ 1,25 Vit D → ↑ Calcium absorption from gut
→ ↓ PTH
→ ↓ renal 1-hydroxylase
→ ↑ renal 24-hydroxylase
(switch to inactive 24-25(OH)₂D₃)
→ ↑ Fibroblast growth factor 23
→ ↓ renal 1-hydroxylase
→ ↓ PO₄ (↑ excretion)

Requesting Lab for Vitamin D Levels

Order 1-25 (OH)D to determine if vit D is high

Order 25(OH)D to determine if vit D is low

Why? Because $[25(\text{OH})\text{D}] \sim 1000\times > [1-25(\text{OH})_2\text{D}]$

Note: Lab must report total 25(OH)D

Total 25(OH)D = 25(OH)D₂ + 25(OH)D₃

So what?

In humans >99% is D₃, but; if the person is on D₂ therapy, ~55% is D₂ and ~45% is D₃

What are Normal Vitamin D Levels?

What the cut points that define vit D levels

Normal	32-100 ng/mL ¹
Insufficient	10- <32 ²
Deficient	<10 ²

A normal level of vit D is based on measurements in sun exposed individuals

50-75% of population have levels <30 ng/mL

20-35% have levels <20 ng/mL³⁻⁵

1. Hollis BW, Wagner CL. NEJM 2005;352:515
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What Are the Consequences of Low Vitamin D?

Bone

Rickets has been known for centuries and is associated with vit D levels <10 ng/mL¹

Low vit D ~ 20 ng/mL is associated with hip fractures²

Vit D3 (min dose 800 U/d) reduces fractures $\sim 20\%$ ^{3,4}

Muscle

Muscle pain and weakness is due to atrophy of type II (fast twitch) fibers^{5,6} and is associated with vit D levels <20 ng/mL⁷

Vit D (min dose 800 U/d) reduces risk of falls $\sim 70\%$ ⁸

Vit D levels in those at highest risk <16 ng/mL⁹

What Are the Consequences of Low Vitamin D?

Cancer

Vit D is anti-proliferative, pro-differentiating^{10,11}

Epidemiology studies suggest that higher vit D levels are associated with lower incidence of many cancers and better survival if neoplasia occurs¹²⁻¹⁴

Associations between vit D and cancer^{15,16}

>20 ng/mL 30-50% ↓ colorectal, prostate cancer

>50 ng/mL 50% ↓ breast cancer

Early clinical trials are in progress evaluating the anti-tumor effects of vit D and new D analogs¹⁷

What Are the Consequences of Low Vitamin D?

Kidney

In CKD, $\uparrow\text{PO}_4$ and $\uparrow\text{PTH}$ are universal which leads to mineral-bone disease and calcium deposition in the vasculature, i.e. atherosclerosis^{18,19}

85% of CKD patients have low vit D due to

- i. Decreased renal mass \rightarrow $\downarrow\text{GFR}$
 \rightarrow \downarrow delivery 25(OH)D to 1- α -hydroxylase²⁰
- ii. PO_4 retention induces FGF-23 whose activity is $>\text{PTH}$ \rightarrow \downarrow 1- α -hydroxylase²¹

Heart

Vit D deficient adults have 50% \uparrow risk of MI²²
Vit D may \downarrow BP and LVH by \downarrow RAAS activity²³

What Are the Consequences of Low Vitamin D?

Diabetes

↓vit D → ↑PTH → → ↑Ca → → → ↑ lipolysis (FFA)
→ ↑insulin resistance and ↓insulin release^{24,25}

Prevalence of Metabolic Syndrome Components²⁶

	Vit D Level	
	<20 ng/mL	>40 ng/mL
Metabolic Synd	28%	13%
Abd Obesity	50%	19%
↑TG	30%	24%
↓HDL	40%	30%
↑BP	15%	6%
↑Glucose	34%	24%

References, Consequences of Low Vitamin D

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Should Everyone be Screened to Determine Vit D Levels?

- No current recommendations to screen everyone, however, this may change in the near future
- There is evidence to support screening at-risk people:
 - Osteoporosis
 - Malabsorption (bariatric surgery, Celiac, etc)
 - Hepatic disease
 - Renal disease
 - Patients on anti-seizure drugs
 - Cancer patients (?)
- Unknown: Crohn's, TB, MS, T1D, T2D, CAD

Treating Vit D Insufficiency

Goals

Estimates are based vit D levels where PTH begins increasing, bone density decreases, rates of gut calcium absorption and kinetics of D2 or D3 hydroxylation

- Normal range for vit D is 32-100 ng/mL¹
- 32 ng/mL is accepted as the minimum level²
- Optimum level = ?

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2. Hollis BW, Wagner CL. NEJM 2005;352:515

Preventing Vit D Insufficiency

Major source of vit D is sun exposure¹

Minimum sun exposure for 20,000 units vit D:

2 hour/wk light skin persons²

10-20 hour/wk dark skin persons³

However, life styles world wide have minimized sun exposure to the extent that no variations in vit D levels are now seen in different latitudes⁴

Note: Diet is a poor source of vit D⁵

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Preventing Vit D Insufficiency

Over-the-counter-supplements?

Good luck...potency is unknown, regardless of what the label says

Dose

No consensus on dose for different ages or ethnic groups^{1,2}

Best estimates

Natl Osteoporosis Foundation: 800-1000U/d³

Expert opinion 2000 U/day⁴

Pregnancy 2000 U/d minimum⁵

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Rx for Vit D Insufficiency-Deficiency

- Available vit D Rx

D2 ergocalciferol 50,000 U

8,000 U/mL

D3 cholecalciferol 5,000, 2000, 1000, 400 U

1-25(OH)D3 calcitriol 0.25, 0.5 mcg

Rocaltrol 0.25, 0.5 mcg

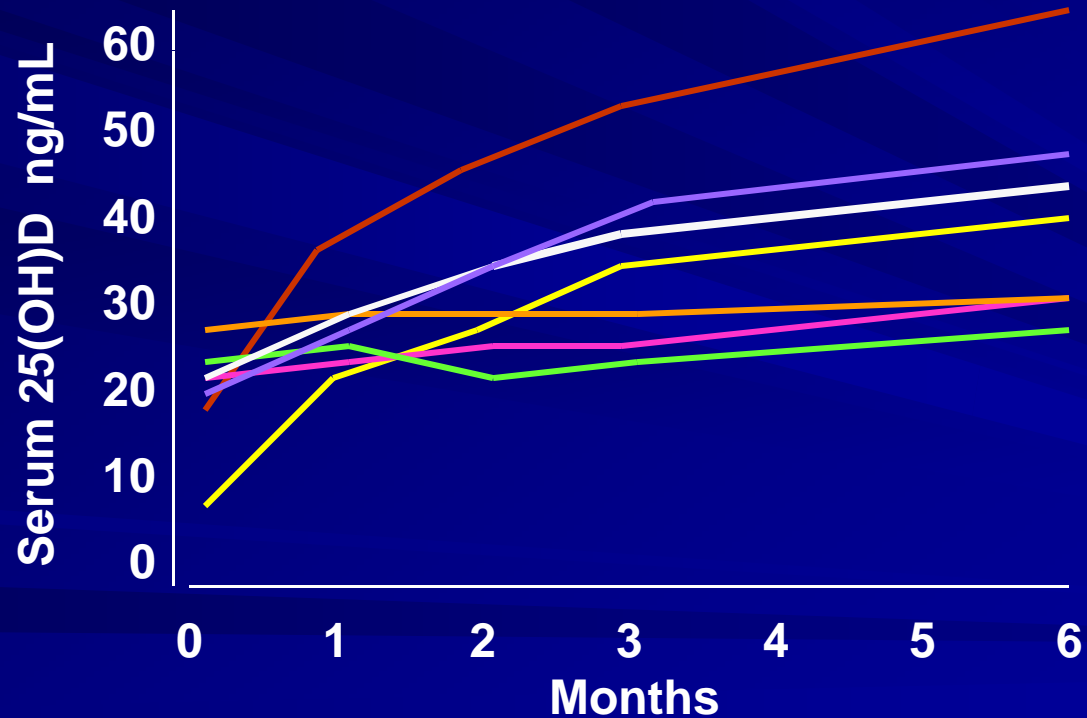
Calcijex 0.5 mcg (IV)

- Use D2 or D3 for insufficiency or deficiency: *Safe!*
- Use 1-25(OH)D in ESRD *Caution: Hypercalcemia*

Note: The analogs doxercalciferol and paricalcitol are only approved for SHPT in CKD III-V

Treating Vit D Insufficiency

Response to therapy is variable¹
(1600 U vit D per day)



1. Binkley N et al. J Bone Miner Res 2008;23(suppl 1):S350

Treating Vit D Insufficiency-Deficiency

Which oral supplement is best, D2 or D3?

- Most studies indicate that D3 is more potent than D2.¹ Some studies demonstrate D2 = D3²
- Currently D2 and D3 are regarded as clinically interchangeable for treating insufficiency or deficiency
- Only high dose form of pro-vit D is ergocalciferol

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Treating Vit D Insufficiency-Deficiency

Vit D regimens

No consensus on best protocol

Ergocalciferol: 50,000 U, 2 days/month
50,000 U, 5 days/month
50,000 U, 1 dose/week
50,000 U, 2 doses/week
50,000 U, 3 doses/week?

Cholecalciferol: 1,000 U, daily
5,000 U, daily

Treating Vit D Insufficiency-Deficiency

Perspectives

600,000 U of D2 over 2 months will increase 25(OH)D levels to >30 ng/mL in 65% of patients¹

50,000 U of D2 per week up to 3 years will increase 25(OH)D levels to >30 ng/mL in ~100% of patients²

Rule of thumb:

1000 U D3 daily will ↑25(OH)D levels by 10 ng/mL³

Note: 50,000 U D2 sounds like a big dose, but know that
50,000 U = 1.25 mg

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2. Ramamurthy R et al. J Clin Densitom 2009;12:375
3. Binkley N. J Bone Miner Res 2008;23(suppl 1)S350

Vit D Toxicity

There is no cut-point defining what level of 25(OH)D should be considered “toxic”¹

Some labs use >80 ng/mL as a toxic level

Some labs use >100 ng/mL as a toxic level

Review of all reports of hypercalcemia due to vit D toxicity report 25(OH)D levels >88 ng/mL

The maximum level of 25(OH)D attained from sun exposure is 70-80 ng/mL^{2,3}

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Monitoring Vit D Therapy

Best way to monitor therapy is not established

Recommendation¹

Check 25(OH)D levels 4-6 months in high-risk patients (osteomalacia, fragility fractures, high-risk falls)

Rationale is that it requires 3-6 months for serum 25(OH)D levels to plateau after starting therapy