To Treat or Not to Treat Vitamin D Deficiency

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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)D 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 calcefediol.
- 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

\[ \downarrow \text{Ca} \rightarrow \uparrow \text{PTH} \]

\[ \uparrow \text{PO}_4 \rightarrow \uparrow \text{PTH} \]

\[ \uparrow \text{PTH} \rightarrow \uparrow \text{renal 1-hydroxylase} \rightarrow \uparrow 1,25 \text{vit D} \]

\[ \uparrow \text{calcium resorption from bone and by kidney} \]

\[ \uparrow 1,25 \text{vit D} \rightarrow \uparrow \text{Calcium absorption from gut} \]

\[ \rightarrow \downarrow \text{PTH} \]

\[ \rightarrow \downarrow \text{renal 1-hydroxylase} \]

\[ \rightarrow \uparrow \text{renal 24-hydroxylase} \]

\[ \text{(switch to inactive 24-25(OH)\textsubscript{2}D3)} \]

\[ \rightarrow \uparrow \text{Fibroblast growth factor 23} \]

\[ \rightarrow \downarrow \text{renal 1-hydroxylase} \]

\[ \rightarrow \downarrow \text{PO}_4 \text{ (\uparrow excretion)} \]
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(OH)D] ~1000x > [1-25(OH)₂D]

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/mL \(^3-5\)

5. Orwoll E et al. J Clin Endocrinol Metab 2009;94:1214
What Are the Consequences of Low Vitamin D?

Bone
Rickets has been known for centuries and is associated with vit D levels <10 ng/mL\(^1\)
Low vit D ~20 ng/mL is associated with hip fractures\(^2\)
Vit D3 (min dose 800 U/d) reduces fractures ~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/mL\(^7\)
Vit D (min dose 800 U/d) reduces risk of falls ~70\%\(^8\)
Vit D levels in those at highest risk <16 ng/mL\(^9\)
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 occurs $^{12-14}$

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

- $>20 \text{ ng/mL}$ 30-50% ↓ colorectal, prostate cancer
- $>50 \text{ ng/mL}$ 50% ↓ breast cancer

Early clinical trials are in progress evaluating the anti-tumor effects of vit D and new D analogs $^{17}$
What Are the Consequences of Low Vitamin D?

Kidney

In CKD, ↑PO₄ and ↑PTH are universal which leads to mineral-bone disease and calcium deposition in the vasculature, i.e. atherosclerosis¹⁸,¹⁹

85% of CKD patients have low vit D due to

i. Decreased renal mass → ↓GFR
   → ↓ delivery 25(OH)D to 1-α-hydroxlyase²⁰

ii. PO₄ retention induces FGF-23 whose activity is >PTH → ↓ 1-α-hydroxlyase²¹

Heart

Vit D deficient adults have 50% ↑risk of MI²²
Vit D may ↓BP and LVH by ↓RAAS activity²³
What Are the Consequences of Low Vitamin D?

Diabetes

↓vit D → ↑PTH → → ↑Ca → → → ↑lipolysis (FFA)
→ ↑insulin resistance and ↓insulin release

Prevalence of Metabolic Syndrome Components

<table>
<thead>
<tr>
<th>Metabolic Synd</th>
<th>&lt;20 ng/mL</th>
<th>&gt;40 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Synd</td>
<td>28%</td>
<td>13%</td>
</tr>
<tr>
<td>Abd Obesity</td>
<td>50%</td>
<td>19%</td>
</tr>
<tr>
<td>↑TG</td>
<td>30%</td>
<td>24%</td>
</tr>
<tr>
<td>↓HDL</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>↑BP</td>
<td>15%</td>
<td>6%</td>
</tr>
<tr>
<td>↑Glucose</td>
<td>34%</td>
<td>24%</td>
</tr>
</tbody>
</table>
References, Consequences of Low Vitamin D

11. Positive benefit clinicaltrials.gov as NCT00352170
23. Clinicaltrials.gov NCT00497146 and NCT00616902
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/mL\(^1\)
- 32 ng/mL is accepted as the minimum level\(^2\)
- Optimum level = ?

Preventing Vit D Insufficiency

Major source of vit D is sun exposure

Minimum sun exposure for 20,000 units vit D:
- 2 hour/wk light skin persons
- 10-20 hour/wk dark skin persons

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

Note: Diet is a poor source of vit D

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/d\(^3\)
Expert opinion 2000 U/day\(^4\)
Pregnancy 2000 U/d minimum\(^5\)

3. Natl Osteoporosis Foundation 2008
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 doxercalciferal and paricalcitol are only approved for SHPT in CKD III-V
Treating Vit D Insufficiency

Response to therapy is variable\(^1\) (1600 U vit D per day)

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

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 patients

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

Rule of thumb:

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

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

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/mL²,³

1. Vieth R. J Bone Miner Res 2007;22(suppl 2):V64
Monitoring Vit D Therapy

Best way to monitor therapy is not established

Recommendation

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

Binkley N. Endocrinol Metab Clin N Amer 2010;39(2):287