The Dietary Requirement for Vitamin D: Looking Beyond Bone

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Types of Vitamin D

Vitamin D₃:
- Formed by enzymatic degradation of ergosterol
- Found in chicken
- Provided by some dietary sources and multivitamins
- Biologically inert
- Conversion (25OH) in liver and kidneys produces active form
- 25OH is less potent than 1,25D

Vitamin D₆:
- A naturally occurring form in humans
- Formed by action of ultraviolet light on vitamin D3 present in skin
- Present in certain nutrients
- Biologically inert
- Conversion (25OH) in liver and kidneys produces active form

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Within Tissues Processing

Metabolism of Vitamin D Under Conditions of Adequate Vitamin D Supply

When vitamin D supplies are adequate, flow of 25(OH)D through other potential pathways, including its utilization by peripheral tissues for paracrine regulation, is no longer compromised.

Metabolism of Vitamin D Under Conditions of Low Vitamin D Supply

The vessels represent metabolic compartments, stages in the metabolism of vitamin D. The height of the shaded portion of each vessel represents the relative concentration of each metabolite indicated in the figure.

Vitamin D essentially does not occur in natural foodstuffs.
Cutaneous Generation of Vitamin D

How much solar exposure is required to synthesize endogenous vitamin D$_3$?

A single initial MED dose of UVB radiation to a light-skinned individual will release approximately 20,000 IU vitamin D$_3$ into the circulation within 24 hrs.

However, if an individual has very dark skin the exposure time for a MED could increase by 10-fold.
Effect of UVB exposure time and skin colour on Vitamin D production:

<table>
<thead>
<tr>
<th>Yield of vitamin D</th>
<th>White skin</th>
<th>Very Dark skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 min</td>
<td>Same capacity for vit D, different exposure-time requirements</td>
<td></td>
</tr>
<tr>
<td>120 min</td>
<td></td>
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Childhood lack of vitamin D causes rickets

Contracted pelvis, in a case of osteomalacia (adult rickets). Normal childbirth would be impossible.

Normal shape of female pelvis.
Oral Supplementation of Vitamin D

Circulating 25(OH)D as a Function of Oral Vitamin D₃ Intake

Regression of the equilibrium increment in serum 25(OH)D₃ concentration (s, from Eq. 1) on labeled dose for the means of each treatment group.
How toxic is vitamin D?

- The U.S. Nutrition Guidelines state that the lowest observed adverse effect level (LOAEL) for humans is 2,000 IU vitamin D/day.
- This statement is grossly in error and is an impediment to the health of humans.

Optimal Circulating Concentrations of 25(OH)D
Vitamin D Status in Primates and Early Humans

Haddad and Chyu
JCEM 1971, 33: 992-995

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Age (years)</th>
<th>Consumption Of D Weekly (units)</th>
<th>Weekly Exposure to Sunlight (hours)</th>
<th>Plasma 25 – HCC (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Volunteers</td>
<td>40</td>
<td>30.2 ± 12.3</td>
<td>2230 ± 1041</td>
<td>8.8 ± 6.1</td>
<td>27.3 ± 11.8</td>
</tr>
<tr>
<td>Biliary Cirrhosis</td>
<td>4</td>
<td>1.5 - 95</td>
<td>2500 (est.)</td>
<td></td>
<td>6.4 ± 2.5*</td>
</tr>
<tr>
<td>Lifeguards</td>
<td>8</td>
<td>16.5 ± 2.0</td>
<td>2895 ± 677</td>
<td>53.0 ± 16.3</td>
<td>64.4 ± 6.7*</td>
</tr>
</tbody>
</table>

* P < .001
+ values represent mean ± SD

“Normal” Vitamin D Status

- Should NEVER have been defined by Gaussian distribution.
- This is similar to defining “normal” estrogen levels by sampling a population of women whom are primarily postmenopausal.

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Biomarkers for Vitamin D Sufficiency

- 25(OH)D
- Intact PTH
- Bone Mineral Density (BMD)
- Intestinal Calcium Absorption
- Mobility responsiveness
- Insulin sensitivity
- Beta cell function
- Immune function
- Circulating cytokines

Activation of human TLR2/1 triggers a vitamin D receptor-dependent antimicrobial response


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Vitamin D and the Innate Immune System

- In 1903, Niels Ryberg Finsen was awarded the Nobel Prize for his work, demonstrating that UV light was beneficial to patients with Lupus vulgaris.
- The beneficial effects of UV exposure to tuberculosis patients is also known.
Rickets and Infection

- Rickets is not only associated with skeletal abnormalities but also respiratory infections.
- In 1994 a brief study demonstrated that respiratory infections in children with elevated alkaline phosphatase levels were eliminated by supplementing them with 60,000 IU vitamin D/wk for a period of 6 wks.

Addition of 25D3 restores ability of sera from African American individuals to support TLR2/1L mediated induction of cathelicidin mRNA

<table>
<thead>
<tr>
<th>25D3 (nmol/L)</th>
<th>Fold Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>25</td>
<td>2 ± 0.1</td>
</tr>
<tr>
<td>50</td>
<td>5 ± 0.2</td>
</tr>
<tr>
<td>75</td>
<td>7 ± 0.3</td>
</tr>
<tr>
<td>100</td>
<td>10 ± 0.4</td>
</tr>
<tr>
<td>125</td>
<td>12 ± 0.5</td>
</tr>
<tr>
<td>150</td>
<td>15 ± 0.6</td>
</tr>
</tbody>
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rickets/osteomalacia
osteoporosis
normal

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Future Implications

- Cancer
- Autoimmune diseases
- Immune dysfunction
- Cardiac health

**Multivariable RR and 95% CI for a 25 nmol/L increment in predicted plasma 25(OH) vitamin D level**

HPFS (1986-2000)

- Brain (91)
- Melanoma (skin) (441)
- Multiple myeloma (97)
- Bladder (360)
- Lung (418)
- Advanced prostate (461)
- Non-Hodgkin's lymphoma (330)
- Kidney (176)
- Colorectal (469)
- Stomach (79)
- Pancreas (170)
- Leukemia (82)
- Esophagus (59)
- Oral / pharyngeal (51)

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It is a well known fact that human milk is a poor source of vitamin D for the nursing infant.

This is an absolutely false and absurd statement.
Conclusions

- Based on biomarkers of nutritional vitamin D status (PTH, BMC, intestinal calcium absorption, insulin sensitivity, beta cell function, and innate immune function), circulating levels of 25(OH)D <32 ng/mL should be considered deficient. What an “optimum level” remains to be determined.
- A 400 IU DRI for vitamin D is irrelevant with respect to the adult population in general.
- Solar exposure as a means to ensure adequate vitamin D status is problematic.
- Guidelines stating that the lowest observed adverse effect level for humans is 2,000 IU vitamin D/day are incorrect. In reality, the AI for adults may be 2,000 IU/day and in some cases such as pregnancy and lactation—higher.
- It is almost certain that chronic nutritional vitamin D deficiency puts populations at risk for developing debilitating, long latency chronic diseases such as cancer and autoimmune disease.
Thank you