Safety of Vitamin D

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safety

1: the condition of being safe from undergoing or causing hurt, injury, or loss

IOM August 4 2009
Safety = Toxicity

For vitamin D, the classic criteria for harm pertain to excessive calcium in serum or urine.

No other harmful outcomes are known... except for some epidemiologic relationships that relate higher serum 25(OH)D to higher risk of prostate and pancreatic cancers.
Safety = Toxicity

The context of calcium excess:
June 1999, a 29-year-old man admitted to emergency with symptoms of:

- extreme right-sided flank pain
- conjunctivitis (a sign of dehydration)
- increased thirst
- vomiting
- in acute renal failure
- anorexia
- fever, chills

Initially treated with steroids and discharged: presumed gastroenteritis
Vitamin D3 Poisoning by Table Sugar.
DOSE: 1.7 MILLION UNITS/DAY FOR 7 MONTHS!

October 1999, his 63-year-old father was admitted to emergency with similar complaints.

He was also in acute renal failure, and no history of stones.

Calcium **VERY HIGH** 3.82 mmol/L (normal, 2.20-2.65 mmol/L),

25(OH)D **HIGH** 1555 nmol/L (normal 20-80 nmol/L)

1,25(OH)₂D **NEAR NORMAL** 151 pmol/L (normal, 30-140 pmol/L)

Elevated “free” 1,25(OH)2D causing toxicity.
Vitamin D3 Poisoning by Table Sugar.
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October 1999, his 63-year-old father was admitted to emergency with similar complaints. He was also in acute renal failure, and no history of stones. Calcium VERY HIGH 3.82 mmol/L (normal, 2.20-2.65 mmol/L), 25(OH)D HIGH 1555 nmol/L (normal 20-80 nmol/L), 1,25(OH)2D NEAR NORMAL 151 pmol/L (normal, 30-140 pmol/L). Elevated “free” 1,25(OH)2D causing toxicity.
Saturability: 25(OH)D > 600 nmol/L

Toxic mechanism involves FREE 1,25(OH)2D

SATURABILITY OF DBP

PLASMA

D-Binding

Protein

(capacity

4300 nmol/L

1800 ng/mL)

PLASMA

VITAMIN D

METABOLITES

BOUND

PLASMA 1,25(OH)2D
BOUND

PLASMA 1,25(OH)2D FREE

BONE CALCIUM RESORPTION

INTESTINE CALCIUM ABSORPTION

Excessive calcium in blood and urine

**Human Dose Response for vitamin D**


**Study Group Mean Data**
**Vit D2-Treated Group Mean Data**
**Individuals with Vit D2 Hypercalcemia**

**Serum 25(OH)D ng/ml**

**400**

**100**

**1000**

**20**

**10**

**200**

**1000**

**4000**

**40,000**

**400,000**

**TANNING**

**UL**

**X = reported toxicity = HYPERCALCEMIA**

**Vitamin D µg/day**

**Vitamin D Intake IU/day**

**Data from literature cited in Vieth 1999, Amer J Clin Nutr, 69:842**
Safety of vitamin D₃ in adults with multiple sclerosis¹–³

Samantha M Kimball, Melanie R Ursell, Paul O’Connor, and Reinhold Vieth

ABSTRACT

Background: Vitamin D₃ may have therapeutic potential in several diseases, including multiple sclerosis. High doses of vitamin D₃ may be required for therapeutic efficacy, and yet tolerability—in the present context, defined as the serum concentration of 24-hydroxyvitamin D [25(OH)D] that does not cause hypercalcemia—remains poorly characterized.

Objective: The objective of the study was to characterize the calcemic response to specific serum 25(OH)D concentrations.

Design: In a 28-wk protocol, 12 patients in an active phase of multiple sclerosis were given 1200 mg elemental Ca/d along with progressively increasing doses of vitamin D₃: from 700 to 7000 μg/wk (from 28 000 to 280 000 IU/wk).

Intakes of 100 μg/d (4000 IU/d) (5) (6) have been shown to be safe. studies suggest that the desirable s [25(OH)D] concentration exceeds and sustain these concentrations in adults require vitamin D intakes of IU/d) (10, 11).

There is much interest in the role of health and disease. The rationale multiple sclerosis (MS) is that metab as paracrine immune modulators (1, 2) for example, proinflammatory T lymphoc production of cytokines, both of which
Doses of vitamin D pertinent to the UL and LOAEL, and their effects on serum calcium

MS Patients on 1200 mc Ca. EVERY MONTH THE VITAMIN D3 DOSE WAS INCREASED IN A STUDY TO CHARACTERIZE TOLERABILITY TO SPECIFIC SERUM 25(OH)D LEVELS.

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**Graph:**


**Axes:**

- **X-axis:** Vitamin D3 Dose Schedule (ug/d)
- **Y-axis:** Serum 25(OH)D (nmol/L)

**Legend:**

- **Baseline**
- **Calcium**
- **100**
- **200**
- **400**
- **800**
- **1,000**

**Data Points:**

- **Serum 25(OH)D ng/ml**
  - 160
  - 80
  - 0
Vitamin D3 Dosing Schedule (ug/d)

Serum Calcium mmol/L

30  50  60  72  80  150  162 fl

25(OH)D ng/mL

Baseline  Calcium  100  200  400  800  1,000

The effect of vitamin D nutrition (based on serum 25(OH)D reaches a plateau at about 80 nmol/L)


Fig. 2. Calcium absorption fraction plotted as a function of serum 25OHD concentration in three studies. The paired ○ symbols represent the data of one study [11]; the paired △ symbols, a second [12], and the □ symbol is the estimated absorption for the subjects not treated with Vitamin D in the study of Bischoff et al. [13,14]. (Copyright Robert P. Heaney, 2003. Used with permission.)
Urine calcium / creatinine ratio vs 25(OH)D

Range to which vitamin D helps increase calcium absorption

Range of no effect on Ca absorption

First evidence that higher 25(OH)D is driving Ca absorption. This is NOT YET TOXIC
Safety = Toxicity

The context of Higher 25(OH)D and Higher Cancer risk
Overall conclusion 6: adverse events

There is no data available on the health hazards of long-term maintenance of high 25-hydroxyvitamin D serum levels in healthy subjects over long periods.

Past experiences with other compounds (e.g., several antioxidants and hormone replacement therapies) have shown serious adverse effects of the chronic use of supplements or long-term maintenance of high serum levels.
<table>
<thead>
<tr>
<th>Study</th>
<th>Category</th>
<th>25(OH)D concentration (nmol/L)</th>
<th>P for trend</th>
<th>Quality</th>
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</thead>
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<tr>
<td>Ahn 2008</td>
<td>Q1 (ref)</td>
<td>13 - 43</td>
<td>0.20</td>
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<tr>
<td>(n=1530)</td>
<td>Q2</td>
<td>43 - 51</td>
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<td></td>
<td>Q3</td>
<td>51 - 61</td>
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<tr>
<td></td>
<td>Q4</td>
<td>61 - 72</td>
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<td></td>
<td>Q5</td>
<td>72 - 129</td>
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<td>(n=920)</td>
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<td>Q3</td>
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<td>Q3</td>
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Table 29. Vitamin D and pancreatic cancer: Results of observational studies

<table>
<thead>
<tr>
<th>Year</th>
<th>Life Stage, y</th>
<th>Outcome (no. of cases; no. of control)</th>
<th>Time to diagnosis, y</th>
<th>25(OH)D concentration, nmol/L</th>
<th>No. of cases</th>
<th>No. of control</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P for trend</th>
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<td>1971</td>
<td>51-70, male only</td>
<td>Exocrine pancreatic cancer (200; 400)</td>
<td>11.6 (median)</td>
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<td>41-51.1</td>
<td>47</td>
<td>80</td>
<td>2.12</td>
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<td>51.1-60.5</td>
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<td>81</td>
<td>1.50</td>
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<td>60.5-65.5</td>
<td>57</td>
<td>79</td>
<td>2.92</td>
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<td>Exocrine pancreatic cancer (200; 400)</td>
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<td>&gt;65.5</td>
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<tr>
<td>1971</td>
<td>51-70, both sexes</td>
<td>Pancreatic cancer (184; 368)</td>
<td>5.4 (median), up to 11 y</td>
<td>&lt;45.9</td>
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<td>&gt;72.3</td>
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<td>55.2 to 61.4</td>
<td>21</td>
<td>43</td>
<td>2.33</td>
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<td>Pancreatic cancer: Moderate residential sun exposure area (91; 157)</td>
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<td>&gt;61.4</td>
<td>25</td>
<td>38</td>
<td>1.03</td>
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<td>48</td>
<td>1.97</td>
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*Statistically significant (P<0.05)
Evidence Report/Technology Assessment
Number 183 Vitamin D and Calcium: A Systematic Review of Health Outcomes
Prepared for: Agency for Healthcare Research and Quality

Low UV
P=0.015

High UV

Serum 25(OH)D nmol/L

Stolzenberg-Solomon 2009
SAME AVERAGE 25(OH)D BUT Larger amplitude results in larger below-setpoint phase in tissue 1,25(OH)2D

Shaded area highlights the sub-setpoint phases in tissue 1,25(OH)2D.
Higher 25(OH)D would **dampen** negative effects of seasonal variation:

*Shaded area highlights the sub-setpoint phases in tissue 1,25(OH)2D.*
For vitamin D, the classic criteria for harm pertain to excessive calcium in serum or urine.  **TOXICITY REQUIRES AVERAGE DAILY INTAKES WELL BEYOND 10,000 IU**

Northern or low-UV environments: epidemiologic relationships with higher serum 25(OH)D and higher risk of prostate and pancreatic cancers. These may be due to **seasonal high/low fluctuations in 25(OH)D** that may be alleviated with vitamin D supplementation.