Treatment & Toxicity – Benefits and dangers of supplementing with Vitamin D.

Reinhold Vieth
Professor, Departments of Nutritional Sciences and Laboratory Medicine and Pathobiology, University of Toronto, and Pathology, Mount Sinai Hospital, Toronto, Canada

LONDON APRIL 7, 2011
Full-skin exposure to summer sun
= 10,000 IU daily of vitamin D3
= 250 mcg/day
Paraphrasing Paraclesius:  
“anything that actually works, will be harmful if the dose is high enough”
25-OH-D Thresholds

IOM-2011 SUGGESTED THRESHOLD = 50 nmol/L (20 ng/ml)

Plasma 25-OH-D (nmol/l)

- Insufficiency
- Sufficiency
- Toxicity

Deficiency  Sufficiency?  Toxicity

Acute Toxicity >200 ng/mL

Normal Function (%)

Plasma 25-OH-D (nmol/l)

50  125  250
Traditionally

• Vitamin D safety is defined by the absence of hypercalcemia or hypercalciuria.
In 1924, Hess and Weil reported the results of a study in which it was found that administration of cod-liver oil for 6 months'
 minimum 46000 IU/d for weeks.

**Table 1**

**Summary of Published Series**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Preparation of vitamin D</th>
<th>Daily dose per kg body-weight (approx.)</th>
<th>Period of treatment</th>
<th>Toxic symptoms</th>
<th>Renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Irradiated</td>
<td>50,000-5,000</td>
<td>8 weeks</td>
<td>1 (16%)</td>
<td>Yes</td>
</tr>
<tr>
<td>None</td>
<td>Ergosterol</td>
<td>7,000-10,000</td>
<td>1-12 weeks</td>
<td>1 (16%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Two with no disease</td>
<td>Vigantol</td>
<td>10,000-12,000</td>
<td>6-15 days</td>
<td>3 (100%)</td>
<td>Yes</td>
</tr>
<tr>
<td>One year</td>
<td>Vigantol</td>
<td>5,000-12,000</td>
<td>6-15 days</td>
<td>3 (100%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Vigantol</td>
<td>40,000-12,000</td>
<td>1 day</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Vigantol</td>
<td>200,000-12,000</td>
<td>1 day</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Post-operative tetany, habi-ferner, arthritis, miscellaneous, and normal subjects</td>
<td>Vitamin D in corn oil</td>
<td>1,600-3,000</td>
<td>87 days</td>
<td>26 (45%)</td>
<td>No data</td>
</tr>
<tr>
<td>Rheumatoid arthritis and other types of arthritis</td>
<td>Vitamin D2 in oil or propyl glycol</td>
<td>48,000-80,000</td>
<td>7 weeks</td>
<td>13 (71%)</td>
<td>Not investigated</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Not specified</td>
<td>160,000-2,300</td>
<td>Weeks to 14 years</td>
<td>None</td>
<td>No data</td>
</tr>
<tr>
<td>No diagnoses given</td>
<td>Irradiated ergosterol</td>
<td>20,000-4,000</td>
<td>Several months</td>
<td>4 (100%)</td>
<td>Yes in 3 months</td>
</tr>
<tr>
<td>Arthritis</td>
<td>8-15 months</td>
<td>20,000-4,000</td>
<td>4 to 18 months</td>
<td>8 (34%)</td>
<td>No data</td>
</tr>
<tr>
<td>Arthritis</td>
<td>8-15 months</td>
<td>20,000-4,000</td>
<td>'Months'</td>
<td>8 (22%)</td>
<td>No data</td>
</tr>
<tr>
<td>Arthritis</td>
<td>8-15 months</td>
<td>20,000-4,000</td>
<td>'Months'</td>
<td>8 (22%)</td>
<td>No data</td>
</tr>
<tr>
<td>Osteoarthritis or fibrositis</td>
<td>Ertron</td>
<td>50,000-750</td>
<td>'Months'</td>
<td>1 (12%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Ertron</td>
<td>200,000-3,000</td>
<td>'Months'</td>
<td>1 (12%)</td>
<td>Yes</td>
</tr>
</tbody>
</table>
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: presumpted gastroenteritis
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.
Calcium input

(Blood) Plasma Calcium

The Kidney functions as an outlet control valve to regulate the Calcium level in the bloodstream.

With Vitamin D toxicity, 1\textsuperscript{ST} Urine Calcium goes up. Later Serum Ca

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

A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis

ABSTRACT

Objective: Low vitamin D status has been associated with multiple sclerosis (MS) prevalence and risk, but the therapeutic potential of vitamin D in established MS has not been explored. Our aim was to assess the tolerability of high-dose oral vitamin D and its impact on biochemical, immunologic, and clinical outcomes in patients with MS prospectively.

Methods: An open-label randomized prospective controlled 52-week trial matched patients with MS for demographic and disease characteristics, with randomization to treatment or control groups. Treatment patients received escalating vitamin D doses up to 40,000 IU/day over 28 weeks to raise serum 25-hydroxyvitamin D (25(OH)D) rapidly and assess tolerability, followed by 10,000 IU/day (12 weeks), and further downtitrated to 0 IU/day. Calcium (1,200 mg/day) was given throughout the trial.

24 PATIENTS, 12 MONTH PROTOCOL, AVERAGING 12,000 IU/ DAY

Burton et al. Neurology 2010
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.
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 on Ca absorption. This is NOT YET TOXIC
25-OH-D Thresholds

IOM-2011 SUGGESTED THRESHOLD = 50 nmol/L (20 ng/ml)

- Deficiency
- Sufficiency?
- Toxicity

Acute Toxicity >200 ng/mL

Normal Function (%)

Plasma 25-OH-D (nmol/l)

50 100 125 250
The safety of vitamin D

Traditionally
- Vitamin D safety is defined by the absence of hypercalcemia or hypercalciuria.

“Recent concerns”:
- RCT → 25(OH)D 125 nmol/L → More falls and fractures
RCT: vitamin D3 dose, 500,000 IU once per year

MORE FALLS AND FRACTURES AND FALLS IN THE VIT D GROUP!!

Figure 2. Kaplan-Meier Plots of Cumulative Incidence of Time to First Fracture and First Fall

- **Falls**
  - HR, 1.16 (95% CI, 1.05-1.28)
  - $P = .003$

- **Fractures**
  - HR, 1.26 (95% CI, 0.99-1.59)
  - $P = .06$

No. of women
- **Vitamin D** 1131: 588, 382, 77, 22
- **Placebo** 1125: 635, 429, 87, 33

Trial Year
- **Vitamin D**: 1131, 1048, 963, 236, 106
- **Placebo**: 1125, 1050, 985, 253, 115

Sanders et al. JAMA. 2010;303(18):1815-1822
RCT: vitamin D3 dose, 500,000 IU once per year
Effect of a Single Oral Dose of 600,000 IU of Cholecalciferol on Serum Calcitropic Hormones in Young Subjects with Vitamin D Deficiency: A Prospective Intervention Study

Cristiana Cipriani, Elisabetta Romagnoli, Alfredo Sollitani, Iacopo Chiodini, Rita Clerico, Vincenzo Carnevale, Maria Lucia Mascia, Claudia Battista, Raffaella Viti, Mauro Pileri, Cristina Eller-Vainicher, and Salvatore Minisola

Departments of Clinical Sciences (C.C., E.R., M.L.M., S.M.) and Dermatology (R.C.), University of Rome "Sapienza," 00161 Rome, Italy; Units of Endocrinology (A.S., C.B., R.V.), Internal Medicine (V.C.), and Clinical Chemistry (M.P.), Instituto di Ricovero e Cura a Carattere Scientifico (IRCCS) "Casa Sollievo della Sofferenza" Hospital, 71013 San Giovanni Rotondo, Italy; and Department of Medical Sciences (I.C., C.E.-V.), University of Milan, Fondazione Policlinico IRCCS, 20132 Milan, Italy

Context: Effects of vitamin D repletion in young people with low vitamin D status have not been investigated so far.

Objective: We evaluated the effect of a single massive dose of cholecalciferol on calcium metabolism at 3, 15, and 30 d, compared to baseline.

Design and Setting: We conducted a prospective intervention study in an ambulatory care setting.

Participants: Forty-eight young subjects with vitamin D deficiency participated in the study.

Intervention: A single oral dose of 600,000 IU of cholecalciferol was administered to each subject.

Main Outcome Measures: We evaluated serum changes of 25-hydroxyvitamin D [25(OH)D], 1,25-di-hydroxyvitamin D, calcium, and PTH induced by a single load of cholecalciferol.
Effect of a Single Oral Dose of 600,000 IU of Cholecalciferol on Serum Calcitriolik Hormones in Young Subjects with Vitamin D Deficiency: A Prospective Intervention Study

Cristiana Cipriani, Elisabetta Romagnoli, Alfredo Solisiani, Iacopo Chiodini, Rita Clerico, Vincenzo Carnevale, Maria Lucia Mascia, Claudia Battista, Raffaella Viti, Mauro Pilani, Cristina Eller-Vainicher, and Salvatore Minisola

Departments of Clinical Sciences (C.C., E.R., M.L.M., S.M.) and Dermatology (R.C.), University of Rome “Sapienza,” 00161 Rome, Italy; Units of Endocrinology (A.S., C.B., R.V.), Internal Medicine (V.C.), and Clinical Chemistry (M.P.), Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) “Casa Sollievo della Sofferenza” Hospital, 70133 San Giovanni Rotondo, Italy; and Department of Medical Sciences (I.C., C.E.-V.), University of Milan, Fondazione Policlinico IRCCS, 20132 Milan, Italy

Context: Effects of vitamin D repletion in young people with low vitamin D status have not been investigated so far.

Objective: We evaluated the effect of a single massive dose of cholecalciferol on calcium metabolism at 3, 15, and 30 d, compared to baseline.

Design and Setting: We conducted a prospective intervention study in an ambulatory care setting.

Participants: Forty-eight young subjects with vitamin D deficiency participated in the study.

Intervention: A single oral dose of 600,000 IU of cholecalciferol was administered to each subject.
In New Zealand, 36 deg South Latitude, Fracture Rates cycle annually even without ice and snow.

Musculoskeletal Health:
Fractures and falls happened with 125 nmol/L (50 ng/mL) because of the ANNUAL dosing protocol.

Basic Pharmacology of vit D:
1. dosing intervals up to 3 months are appropriate.
2. One year’s total dose once annually is "TOXIC". → more falls and fractures
HOW SHOULD A LARGE, LOADING DOSE OF VITAMIN D BE USED?

A “loading dose” is only meaningful if in the context of its appropriate maintenance dose.
“the drug half-life in the central compartment has a direct and significant impact on the appropriate dosing interval for the drug.”

Goodman & Gilman's The Pharmacological Basis of Therapeutics - 11th Ed. (2006)

Fundamental pharmacokinetic relationships for repeated administration of drugs.

Functional half-life for vitamin D = 2 months
A Loading Dose is the amount that fills the central compartment for the drug.

= serum level X volume of distribution

... or = cumulative steady state dose given during one half-life
The safety of vitamin D

Traditionally
• Vitamin D safety is defined by the absence of hypercalcemia or hypercalciuria.

“Recent concerns”:
• RCT → 25(OH)D 125 nmol/L → More falls and fractures

• U-shaped risk curves in relation to serum 25(OH)D.
U-SHAPED RISK CURVE FOR PROSTATE CANCER


Pentti TUOHIMAA1*, Leena TENKANEN2, Merja AHONEN1, Sonja LUMME2, Egil JELLUM3, Göran HALLMANS4, Paör STATIN5, Sverre HARVEI6, Timo HAKULINEN7, Tapio LUOSTARINEN7, Joakim DILLNER8, Matti LEHTINEN9 and Matti HAKAMA10

1Medical School, University of Tampere, Tampere, Finland

**TABLE III – OR AND 95% CI OF PROSTATE CANCER BY 25(OH)-VITAMIN D LEVEL AND COUNTRY**

<table>
<thead>
<tr>
<th>Vitamin D level (nmol/l)</th>
<th>Number of cases</th>
<th>OR (CI)</th>
<th>Number of cases</th>
<th>OR (CI)</th>
<th>Number of cases</th>
<th>OR (CI)</th>
<th>Number of cases</th>
<th>OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All countries</td>
<td></td>
<td></td>
<td>Norway</td>
<td></td>
<td>Finland</td>
<td></td>
<td>Sweden</td>
<td></td>
</tr>
<tr>
<td>≤ 19</td>
<td>19</td>
<td>1.5 (0.8–2.7)</td>
<td>5</td>
<td>0.9 (0.3–2.8)</td>
<td>13</td>
<td>2.4 (1.1–5.1)</td>
<td>1</td>
<td>1.3 (0.1–12.5)</td>
</tr>
<tr>
<td>20–39</td>
<td>169</td>
<td>1.3 (0.98–1.6)</td>
<td>89</td>
<td>1.2 (0.9–1.7)</td>
<td>68</td>
<td>1.9 (1.1–3.1)</td>
<td>12</td>
<td>0.7 (0.3–1.4)</td>
</tr>
<tr>
<td>40–59 (ref.)</td>
<td>229</td>
<td>1</td>
<td>155</td>
<td>1</td>
<td>29</td>
<td>1</td>
<td>45</td>
<td>1</td>
</tr>
<tr>
<td>60–79</td>
<td>138</td>
<td>1.2 (0.9–1.5)</td>
<td>98</td>
<td>1.2 (0.8–1.7)</td>
<td>18</td>
<td>1.4 (0.7–2.8)</td>
<td>22</td>
<td>1.0 (0.5–1.8)</td>
</tr>
<tr>
<td>≥80</td>
<td>67</td>
<td>1.7 (1.1–2.4)</td>
<td>57</td>
<td>1.8 (1.1–2.8)</td>
<td>4</td>
<td>1.2 (0.4–3.8)</td>
<td>6</td>
<td>1.5 (0.5–4.4)</td>
</tr>
</tbody>
</table>

Odds Ratio for Prostate Cancer

25(OH)D nmol/L

<19  | 30  | 50 nmol/L | 70  | >80
Effect of environmental ultraviolet light on the relationship between baseline serum 25(OH)D concentration and the odds of pancreatic cancer.

Data from Table 4 of Stolzenberg-Solomon et al. (Cancer Res 2009;69(4):1439–47) who reported that among subjects residing in regions of low estimated annual ultraviolet light B [UVB] exposure, higher 25(OH)D concentrations were positively associated with pancreatic cancer.
IOM Figures of U-Shaped Risk for MORTALITY

Figure 1. Restricted cubic spline showing the fully adjusted associations between serum 25-hydroxyvitamin D (25(OH)D) levels and all-cause mortality in 18,894 residents of the New Mexico Health and Aging Study.
“U-Shaped Risk Curves”

• They relate to serum 25(OH)D, NOT vitamin D supplementation (unless annual doses)
• They can occur in regions with large seasonal fluctuations in UVB light and serum 25(OH)D
• The mechanism involves inappropriate breakdown of 25(OH)D and 1,25(OH)2D inside of cells, because of difficulty in turning off CYP24 enzyme
1. U-shaped 25(OH)D risk curves are specific to high latitudes.

2. Large pulse doses cause adverse, toxic effects. (RCT to “prove” this would be unethical)
Higher Latitude not only lowers total UVB for vitamin D production, but also INCREASES UVB FLUCTUATIONS

The human “normal”

Perpetually rising and falling 25(OH)D levels are adverse, and explain U-shaped risk curves for vitamin D.

Humans “designed” through natural selection to have steady, levels around 150 nmol/L.

Many modern humans suffer annual cycles of 25(OH)D fluctuation that our species was never designed to experience.

Modern Humans often have 25(OH)D levels around 50 nmol/L.

R Vieth, ANTICANCER RESEARCH 29: 3675-3684 (2009)
## Highest 25(OH)D quartiles, and their Risk differences for Prostate and Pancreatic cancers: RELATIONSHIPS WITH LATITUDE

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>CANCER</th>
<th>LATITUDE</th>
<th>SLOPE</th>
<th>IOM</th>
<th>CASES</th>
<th>CONTROLS</th>
<th>WEIGHTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuohiima</td>
<td>prostate</td>
<td>61.00</td>
<td>0.50</td>
<td>622.00</td>
<td>1,451.00</td>
<td>2,073.00</td>
<td></td>
</tr>
<tr>
<td>Ahonen</td>
<td>prostate</td>
<td>60.00</td>
<td>0.20</td>
<td>149.00</td>
<td>566.00</td>
<td>715.00</td>
<td></td>
</tr>
<tr>
<td>Michaels</td>
<td>allcancer</td>
<td>58.00</td>
<td>0.08</td>
<td></td>
<td></td>
<td>1,194.00</td>
<td></td>
</tr>
<tr>
<td>Stolzenb</td>
<td>pancreat</td>
<td>61.00</td>
<td>0.08</td>
<td>200.00</td>
<td>400.00</td>
<td>600.00</td>
<td></td>
</tr>
<tr>
<td>Stolzenb</td>
<td>pancreat</td>
<td>43.00</td>
<td>0.05</td>
<td>463.00</td>
<td>635.00</td>
<td>1,098.00</td>
<td></td>
</tr>
<tr>
<td>Stolzenb</td>
<td>pancreat</td>
<td>33.00</td>
<td>0.00</td>
<td>489.00</td>
<td>698.00</td>
<td>1,187.00</td>
<td></td>
</tr>
<tr>
<td>Ahn et.</td>
<td>prostate</td>
<td>35.00</td>
<td>-0.15</td>
<td>741.00</td>
<td>781.00</td>
<td>1,522.00</td>
<td></td>
</tr>
<tr>
<td>Jacobs</td>
<td>prostate</td>
<td>33.00</td>
<td>0.04</td>
<td>83</td>
<td>166</td>
<td>249.00</td>
<td></td>
</tr>
<tr>
<td>Li</td>
<td>prostate</td>
<td>35.00</td>
<td>0.00</td>
<td>492.00</td>
<td>664.00</td>
<td>1,156.00</td>
<td></td>
</tr>
<tr>
<td>Platz</td>
<td>prostate</td>
<td>36.00</td>
<td>0.42</td>
<td>460.00</td>
<td>460.00</td>
<td>920.00</td>
<td></td>
</tr>
<tr>
<td>Nomura</td>
<td>prostate</td>
<td>21.00</td>
<td>0.00</td>
<td>136.00</td>
<td>136.00</td>
<td>272.00</td>
<td></td>
</tr>
</tbody>
</table>
Highest 25(OH)D quartiles, and their Risk differences for Prostate and Pancreatic cancers: RELATIONSHIPS WITH LATITUDE

SLOPE

Change in Odds Ratio for Disease between highest 2 Quintiles in 25(OH)D

Latitude of Cohort Studied
Conclusions

1. “Normal” 25(OH)D levels during our evolution ranged between 75-225 nmol/L. These levels are safe and optimal because we were “designed” for this by the process of evolution.

2. There is NO RISK of until much more than 4000 IU (100MCG) average per day is consumed.

Data from literature cited in Vieth 1999, Amer J Clin Nutr 69:842
additional studies, Vieth, J Nutr Environmental Med, Dec 2001
Meta-analysis of data on all-cause MORTALITY in randomized controlled trials with vitamin D.

Study Therapy PLACEBO
Chapuy et al, 1992 258/1634 274/1636
Lips et al, 1996 223/1291 251/1287
Chapuy et al, 2002 71/393 45/190
Meyer et al, 2002 169/569 163/575
Trivedi et al, 2003 224/1345 247/1341
Porthouse et al, 2005 57/1321 68/1993
RECORD Trial, 2005 438/2649 460/2643
Flicker et al, 2004 76/312 85/313
Jackson et al, 2006 744/18176 807/18106

Vitamin D clinical trials ended up showing LOWER mortality than Placebo.

Summary relative risk (95%). 0.92 (0.86-0.99)

Autier and Gandi 2007 Arch Intern Med;167(16):1730-1737
CLOSING COMMENTS

1. The IOM insisted only on “causal” health relationships with vitamin D. i.e. ONLY placebo-controlled clinical trials will do.

2. The IOM concluded that only bone health had “compelling” evidence to support it.

3. Even if one accepts the IOM’s criteria, the IOM 25(OH)D targets do not make sense.

4. The IOM document was NOT peer reviewed.

5. “Consensus” of experts was achieved by excluding advocates.