Vitamin D: The Good, the Bad and the Ugly

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Conflict of Interest Statement - Corporate

- NO STOCKS or EQUITY
- Editor- UpToDate, New England Journal of Medicine, and Endocrine Reviews
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- Speakers bureaus
  - None
  - no consulting fees
Conflicts of Interest

The views expressed in this talk represent my personal interpretation of the IOM report and not officially those of the committee or any member or staff associate

Outline

• The Vitamin D paradox
  – Little evidence, widespread usage

• Vitamin D: Bone
  – Evidence for or against Vitamin D and Musculoskeletal health

• What about Vitamin D and cardiovascular health

• Vitamin D, Obesity and Diabetes

• Conclusion
Vitamin D is Big Business

RAISING THE STAKES
Sales of vitamin D in the United States have risen dramatically in the past decade.

2001 US$40 MILLION
2005 US$50 MILLION
2009 US$425 MILLION

2015 3.3 billion

Testing Vitamin D is Big Business: Vitamin D Monthly Test Volumes Endocrine Lab Rochester, 2004-2010

25-hydroxy vitamin D
1,25-dihydroxy vitamin D
The State of Vitamin D Testing and Interpretation

Is there truly a vitamin D epidemic?

Prevalence of Vitamin D Levels from Commercial Lab

Mayo’s Experience

5 year pattern has changed very little
MAGICAL THINKING

Vitamin D and Implications for Health

Hollis et al 2013

doi: 10.1210/jc.2013-2653

Hollis et al 2013

Vitamin D and Tissue Homeostasis

Diet + UV

Liver

Prohormone

25(OH)D

Ketogenesis

5 weeks

Placenta

Breast, Colon, Skin, Brain, Ovary, Prostate, etc;

25 hydroxylase

25(OH)D

Active Hormones

1,25(OH)\textsubscript{2}D

(regulation)

VDR

Regulation of Cell Growth

Bone

Health

Increased Calcium Absorption

Diet

Milk

Kidney

Active Hormone

1,25(OH)\textsubscript{2}D

2 hrs

1-α hydroxylase

Milk

megalin-mediated

megalin-mediated
Hormones circulating bound to albumin or circulating in a free form (collectively known as Bioavailable Vitamin D) are more readily available to enter cells than hormones bound to their traditional binding proteins.

Vitamin D Binding Protein- Re-emerging

1. ‘Bioavailable’ D is consistent with other hormones

Does DBP concentration vary by ethnicity?

<table>
<thead>
<tr>
<th>Study</th>
<th>African Americans</th>
<th>White Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al, 2014</td>
<td>152 ± 107 (SD)</td>
<td>301 ± 210 (SD)</td>
</tr>
<tr>
<td>Powe et al, 2013</td>
<td>168 ± 3 (SE)</td>
<td>337 ± 5 (SE)</td>
</tr>
<tr>
<td>Denburg et al, 2013</td>
<td>100</td>
<td>240</td>
</tr>
<tr>
<td>Bhan et al, 2012</td>
<td>75</td>
<td>189</td>
</tr>
<tr>
<td>Powe et al, 2011</td>
<td>144 ± 102 (SE)</td>
<td>248 ± 122 (SE)</td>
</tr>
<tr>
<td>Winters et al, 2009</td>
<td>491 ± 128 (SD)</td>
<td>529 ± 202 (SD)</td>
</tr>
<tr>
<td>Bouillon et al, 1977</td>
<td>329 ± 54 (Zaire/Congo)</td>
<td>329 ± 43 (Belgium)</td>
</tr>
</tbody>
</table>

* Ethnic difference P<0.05
** No ethnic difference
Summary

- Vitamin D circulates in the 25OHD form although 1,25OHD is also in the circulation and is the active compound
- 25OHD is bound to D binding protein (DBP) and albumin
- Dissociation of 25OHD from DBP may determine cellular action
- D binding protein assays are still being validated, but it is possible that there are no differences in DBP
What Supports the Widespread Use of Vitamin D?

- Evidence from clinical trials
- Observational data
- Expert opinion
- Case Reports
- Magical Thinking

IOM: Potential Indicators of Health Outcomes for Nutrient Adequacy for Calcium and Vitamin D

- Cancer/neoplasms
- Cardiovascular diseases and Hypertension
- T2D and metabolic Syndrome
- Falls
- Immune Response
- Neuropsychologic functioning
- Physical Performance
- Preeclampsia of pregnancy

- **Skeletal Health-only + evidence**
So What is the evidence for Vitamin D and Fractures?

There are now almost 2 meta-analyses published for every 1 RPCT of calcium/vitamin D and fracture risk.
Vitamin D and Calcium Reduces Fracture Risk (800IU+1200 mg/d)  
Tang Lancet 2007

USPSTF: No Risk Reduction for Vitamin D and Hip Fracture- 2014

Vitamin D Does Not Increase BMD

Reid et al Lancet October, 2013
A Closer Look at the Randomized Controlled Trials

Calcium plus Vitamin D Supplementation and the Risk of Fractures

<table>
<thead>
<tr>
<th></th>
<th>Ca 1000mg+400 IU D</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium supplementation ≥500 mg/day — no. (%)</td>
<td>5,192 (28.6)</td>
<td>5,313 (29.3)</td>
</tr>
<tr>
<td>Total calcium intake (supplements, diet, and medications)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean — mg/day</td>
<td>1148±654</td>
<td>1154±658</td>
</tr>
<tr>
<td>&lt;800 mg/day — no. (%)</td>
<td>6,104 (33.6)</td>
<td>6,003 (31.2)</td>
</tr>
<tr>
<td>800 to &lt;1200 mg/day — no. (%)</td>
<td>4,715 (25.9)</td>
<td>4,655 (25.7)</td>
</tr>
<tr>
<td>≥1200 mg/day — no. (%)</td>
<td>7,002 (38.5)</td>
<td>7,095 (39.2)</td>
</tr>
<tr>
<td>Total vitamin D intake (supplements and diet)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean — IU/day</td>
<td>365±265</td>
<td>368±266</td>
</tr>
<tr>
<td>&lt;200 IU/day</td>
<td>6,827 (37.6)</td>
<td>6,671 (36.8)</td>
</tr>
<tr>
<td>200 to &lt;400 IU/day</td>
<td>3,379 (18.6)</td>
<td>3,423 (18.9)</td>
</tr>
<tr>
<td>400 to &lt;600 IU/day</td>
<td>4,188 (23.0)</td>
<td>4,295 (23.7)</td>
</tr>
<tr>
<td>≥600 IU/day</td>
<td>3,427 (18.9)</td>
<td>3,364 (18.6)</td>
</tr>
</tbody>
</table>
### Table 2. Effect of Calcium with Vitamin D Supplementation on Clinical Outcomes, According to Randomly Assigned Group.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Calcium + Vitamin D</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intention-to-treat analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up time — yr</td>
<td>7.0±1.4</td>
<td>7.0±1.4</td>
<td></td>
</tr>
<tr>
<td>Rate of fracture — no. of cases (annualized %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>175 (0.14)</td>
<td>199 (0.16)</td>
<td>0.88 (0.72–1.08)</td>
</tr>
<tr>
<td>Clinical vertebral</td>
<td>181 (0.14)</td>
<td>197 (0.15)</td>
<td>0.90 (0.74–1.10)</td>
</tr>
<tr>
<td>Lower arm or wrist</td>
<td>565 (0.44)</td>
<td>557 (0.44)</td>
<td>1.01 (0.90–1.14)</td>
</tr>
<tr>
<td>Total</td>
<td>2102 (1.64)</td>
<td>2158 (1.70)</td>
<td>0.96 (0.91–1.02)</td>
</tr>
<tr>
<td><strong>Analysis excluding follow-up time for participants 6 mo after nonadherence detected</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up time — yr</td>
<td>3.8±2.9</td>
<td>3.9±2.9</td>
<td></td>
</tr>
<tr>
<td>Rate of fracture — no. of cases (annualized %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>68 (0.10)</td>
<td>99 (0.14)</td>
<td>0.71 (0.52–0.97)</td>
</tr>
<tr>
<td>Clinical vertebral</td>
<td>91 (0.13)</td>
<td>104 (0.15)</td>
<td>0.89 (0.67–1.19)</td>
</tr>
<tr>
<td>Lower arm or wrist</td>
<td>312 (0.45)</td>
<td>308 (0.43)</td>
<td>1.05 (0.90–1.23)</td>
</tr>
<tr>
<td>Total</td>
<td>1119 (1.63)</td>
<td>1222 (1.72)</td>
<td>0.94 (0.87–1.02)</td>
</tr>
</tbody>
</table>

### Risk of Hip Fracture by Age Group in WHI: Age and Fall Interaction

<table>
<thead>
<tr>
<th>Overall</th>
<th>175 (0.14)</th>
<th>199 (0.16)</th>
<th>0.88 (0.72–1.08)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group at screening — yr</td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>50 to 59</td>
<td>28 (0.06)</td>
<td>13 (0.03)</td>
<td>2.17 (1.13–4.18)</td>
</tr>
<tr>
<td>60 to 69</td>
<td>53 (0.09)</td>
<td>71 (0.13)</td>
<td>0.74 (0.52–1.06)</td>
</tr>
<tr>
<td>70 to 79</td>
<td>93 (0.44)</td>
<td>115 (0.54)</td>
<td>0.82 (0.62–1.08)</td>
</tr>
<tr>
<td>No. of falls in past 12 mo</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>87 (0.11)</td>
<td>117 (0.15)</td>
<td>0.74 (0.56–0.98)</td>
</tr>
<tr>
<td>1</td>
<td>39 (0.16)</td>
<td>41 (0.17)</td>
<td>0.96 (0.62–1.49)</td>
</tr>
<tr>
<td>2</td>
<td>22 (0.22)</td>
<td>19 (0.19)</td>
<td>1.16 (0.63–2.16)</td>
</tr>
<tr>
<td>≥3</td>
<td>16 (0.32)</td>
<td>6 (0.12)</td>
<td>2.51 (0.97–6.48)</td>
</tr>
<tr>
<td>Assignment in Hormone Therapy trial</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>67 (0.24)</td>
<td>61 (0.22)</td>
<td>1.15 (0.81–1.63)</td>
</tr>
<tr>
<td>Active hormone therapy</td>
<td>28 (0.10)</td>
<td>49 (0.17)</td>
<td>0.58 (0.37–0.93)</td>
</tr>
</tbody>
</table>
Chapuy et al NEJM 1992

- 1200 mg Ca + 800 IU Vitamin D
- Nursing home patients (n=1600)
- RPCT-
- 33% reduction in hip fractures

### Table 5. Serum Biochemical Values in the Vitamin D₃—Calcium and Placebo Groups at Base Line and after 6, 12, and 18 Months of Follow-up.*

<table>
<thead>
<tr>
<th>Serum Index and Group</th>
<th>Base Line</th>
<th>6 MO</th>
<th>12 MO</th>
<th>18 MO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dl)†</td>
<td>9.17±0.36</td>
<td>9.28±0.35</td>
<td>9.20±0.33</td>
<td>9.21±0.39</td>
</tr>
<tr>
<td>Vitamin D₃—calcium</td>
<td>9.15±0.40</td>
<td>9.15±0.36</td>
<td>9.00±0.39†</td>
<td>9.00±0.35‡</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.15±0.40</td>
<td>9.15±0.36</td>
<td>9.00±0.39†</td>
<td>9.00±0.35‡</td>
</tr>
<tr>
<td>PTH (pg/ml)§</td>
<td>54±37</td>
<td>35±21†</td>
<td>33±23†</td>
<td>30±14†</td>
</tr>
<tr>
<td>Vitamin D₃—calcium</td>
<td>50±24</td>
<td>50±23</td>
<td>60±30†</td>
<td>56±29†</td>
</tr>
<tr>
<td>Placebo</td>
<td>50±24</td>
<td>50±23</td>
<td>60±30†</td>
<td>56±29†</td>
</tr>
<tr>
<td>25(OH)D (ng/ml)‖</td>
<td>16±11</td>
<td>40±11†</td>
<td>42±9‖</td>
<td>42±9‖</td>
</tr>
<tr>
<td>Vitamin D₃—calcium</td>
<td>13±9</td>
<td>13±9</td>
<td>10±8‡</td>
<td>11±7</td>
</tr>
<tr>
<td>Placebo</td>
<td>13±9</td>
<td>13±9</td>
<td>10±8‡</td>
<td>11±7</td>
</tr>
<tr>
<td>1,25(OH)₂D (pg/ml)‡‡</td>
<td>26±10</td>
<td>ND</td>
<td>ND</td>
<td>27±9</td>
</tr>
<tr>
<td>Vitamin D₃—calcium</td>
<td>29±10</td>
<td>ND</td>
<td>ND</td>
<td>26±9</td>
</tr>
<tr>
<td>Placebo</td>
<td>29±10</td>
<td>ND</td>
<td>ND</td>
<td>26±9</td>
</tr>
<tr>
<td>Alkaline phosphatase  (U/liter)</td>
<td>69±25</td>
<td>60±22†</td>
<td>62±20†</td>
<td>67±22</td>
</tr>
<tr>
<td>Vitamin D₃—calcium</td>
<td>72±22</td>
<td>72±27</td>
<td>79±32††</td>
<td>89±27††</td>
</tr>
<tr>
<td>Placebo</td>
<td>72±22</td>
<td>72±27</td>
<td>79±32††</td>
<td>89±27††</td>
</tr>
<tr>
<td>Osteocalcin (µg/liter)††</td>
<td>8±3</td>
<td>8±3</td>
<td>7±3</td>
<td>7±2</td>
</tr>
<tr>
<td>Vitamin D₃—calcium</td>
<td>8±3</td>
<td>9±3</td>
<td>7±3</td>
<td>8±3</td>
</tr>
<tr>
<td>Placebo</td>
<td>8±3</td>
<td>9±3</td>
<td>7±3</td>
<td>8±3</td>
</tr>
</tbody>
</table>

* 800 IU per day Vitamin D

† n=1490, Placebo=750, Vitamin D₃=740

§ n=1490, Placebo=750, Vitamin D₃=740

‖ n=1490, Placebo=750, Vitamin D₃=740

‡‡ n=1490, Placebo=750, Vitamin D₃=740

†† n=1490, Placebo=750, Vitamin D₃=740
Why Might Vitamin D Supplementation Protect Against Fractures in the Elderly?

Microarchitectural Changes in the Skeleton with Low Vitamin D

Vitamin D Deficiency Induces Early Signs of Aging in Human Bone, Increasing the Risk of Fracture

Björn Busse,1,2* Hrishikesh A. Bale,2 Elizabeth A. Zimmermann,1,2,3 Brian Panganiban,2 Holly D. Barth,2,3 Alessandra Carriero,2 Elke Vettorazzi,5 Josef Zustin,5 Michael Hahn,1 Joel W. Ager III,2 Klaus Püschel,6 Michael Ameling,1 Robert O. Ritchie2,3
Vit D deficiency results in osteomalacia

Cortical Porosity is increased in D Deficiency as is Haversian Canal Diameter and Osteocyte Lacunae Volume
Osteomalacia and Cortical Porosity Are Associated with Micro Cracks and Propagation in Severe Vit D Deficiency

Vitamin D and the Cardiovascular System: Is there benefit?
Biologic Plausibility for Vitamin D Actions on the Vascular System

- 1,25 OH D acts as a differentiation factor in SMC and endothelial cells
- 1,25 OH D induces a favorable cardioprotective gene response in SMC and endothelial cells
- VDR null mice, and 1 alpha hydroxylase null mice have a cardiomyopathy and high renin hypertension
- Vitamin D could limit the inflammatory response in mice (IL-6, CRP, TNF)
- Vitamin D has been shown to improve vascular compliance

Observational Data from Large Cohorts

- Framingham Offspring Study, participants who had a 25(OH)D <15 ng/mL (37.5 nmol/L) were more likely to have their first cardiovascular event during 5.4 years (mean) of observation than those with values ≥15 ng/mL (hazard ratio [HR] 1.62, 95% CI 1.11-2.36)
- In the National Health and Nutrition Examination Study (NHANES) 2001 to 2004, the prevalence of coronary heart disease (angina, myocardial infarction) was more common in adults with 25(OH)D levels <20 ng/mL compared with ≥30 ng/mL (odds ratio [OR] adjusted for age, race, and gender 1.49, 95% CI 1.17-1.91) Adjusting for other risk factors (body mass index, chronic kidney disease, hypertension, diabetes mellitus, smoking, use of vitamin D supplements) attenuated the association (OR 1.24, 95% CI 0.95-1.62).
- In NHANES The prevalence of heart failure and peripheral arterial diseases was also higher among those with 25(OH)D values <20 ng/mL (ORs 2.10 and 1.82, respectively) with similar attenuation after adjustment for other risk factors.
Observational studies identified for the current report found mixed associations between 25(OH)D and total cardiovascular events, cardiovascular death, myocardial infarction, stroke, and fatal stroke.”

Importantly: the WHI Study Failed to Show Cardiovascular Protection With D and Calcium
Vitamin D, Obesity, Type 2 DM

Figure 1. Serum 25(OH)D₃ concentrations (nmol/l) in women (A) and men (B) versus BMI.

ANTICANCER RESEARCH 29: 3713-3720 (2009)
**Vitamin D and insulin action**

![Diagram showing the relationship between Vitamin D, insulin, and glucose metabolism.](image)

**Association of 25OHD with Incident type 2 Diabetes**

Meta-analysis of Longitudinal Observational Studies

↓Risk by 35%

for 25OHD (ng/mL) > 25-30 vs. <8-20

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knekis, FMC, Men</td>
<td>0.49 (0.35-1.64)</td>
</tr>
<tr>
<td>Knekis, FMC, Women</td>
<td>0.91 (0.37-2.23)</td>
</tr>
<tr>
<td>Knekis, MFR, Men</td>
<td>0.17 (0.05-0.57)</td>
</tr>
<tr>
<td>Knekis, MFR, Women</td>
<td>1.45 (0.38-5.62)</td>
</tr>
<tr>
<td>Pitsun, NIES, Women</td>
<td>0.32 (0.33-0.83)</td>
</tr>
<tr>
<td>Robinson, WHB</td>
<td>1.05 (0.62-1.76)</td>
</tr>
<tr>
<td>Grimes, Nurses</td>
<td>0.73 (0.48-1.12)</td>
</tr>
<tr>
<td>Grimes, Smokers</td>
<td>0.68 (0.29-1.61)</td>
</tr>
<tr>
<td>Gagnon, AusChnl</td>
<td>0.56 (0.36-0.86)</td>
</tr>
<tr>
<td>Anderson, Healthcare Population</td>
<td>0.53 (0.43-0.65)</td>
</tr>
<tr>
<td>Bolland, Women</td>
<td>0.90 (0.80-1.00)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.65 (0.52-0.82)</td>
</tr>
</tbody>
</table>

Song et al. (under review)
Pitfalls of Observational Studies with Vitamin D and Type 2 Diabetes

Confounding
Is vitamin D simply a marker of increased risk for type 2 diabetes

Association ≠ “supplementation would be beneficial”

Need

Randomized Clinical Trials

Trials with vitamin D supplementation and type 2 Diabetes related outcomes

8 studies in participants without diabetes
=> no statistically significant effect on measures of glycemia

3 studies in patients with established type 2 Diabetes
=> no statistically significant effect on measures of glycemia
Sugden et al 2008; Jorde and Figenschau 2009; Wilham et al 2010

Studies reviewed by Mnti et al. EJCN 2011
So what’s wrong with taking more vitamin D?

Effect of Vitamin D₃ Supplementation (2,000 IU/day) on Disposition Index (beta-cell function) and HbA₁c

Supported by NIH DK76092

In participants at-risk-for-diabetes

![Graph showing change in Disposition Index and change in hemoglobin A₁c with and without vitamin D supplementation.](image-url)

Mithi et al AJCN 2011
Dose was single annual dose of 500,000 IU (daily equivalent IF/365 = 1370 IU; 

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of Participants</th>
<th>Vitamin D (n = 1131)</th>
<th>Placebo (n = 1125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>76.0 (73.1-80.2)</td>
<td>76.1 (73.0-79.7)</td>
</tr>
<tr>
<td>Baseline risk profile reported by participant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self- or physician-reported high risk of falling</td>
<td>449 (39.7)</td>
<td>429 (38.1)</td>
</tr>
<tr>
<td>Broken bone since age 50 y&lt;sup&gt;1&lt;/sup&gt;</td>
<td>384 (35.5)</td>
<td>343 (32.7)</td>
</tr>
<tr>
<td>Mother had broken hip&lt;sup&gt;1&lt;/sup&gt;</td>
<td>96 (10.0)</td>
<td>99 (10.1)</td>
</tr>
<tr>
<td>Ever used walking aid</td>
<td>204 (25.0)</td>
<td>275 (24.4)</td>
</tr>
<tr>
<td>Baseline calcium intake, mg&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;800</td>
<td>382 (34)</td>
<td>352 (32)</td>
</tr>
<tr>
<td>800–1100</td>
<td>318 (28)</td>
<td>283 (25)</td>
</tr>
<tr>
<td>1101–1300</td>
<td>135 (12)</td>
<td>168 (15)</td>
</tr>
<tr>
<td>&gt;1300</td>
<td>273 (24)</td>
<td>296 (25)</td>
</tr>
<tr>
<td>Biochemical measures, median (IQR)&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-hydroxycholecalciferol, nmol/L</td>
<td>53 (40–66)</td>
<td>45 (40–57)</td>
</tr>
<tr>
<td>PTH, pmol/L</td>
<td>4.2 (2.9–7.0)</td>
<td>5.0 (3.7–8.8)</td>
</tr>
</tbody>
</table>

Abbreviations: IF = intervertebral, PTH = parathyroid hormone.

High Dose Vitamin D increases serum levels of 25OHD levels in 75-125 nmol range

Sanders et al., 2010
Figure 2. Kaplan-Meier Plots of Cumulative Incidence of Time to First Fracture and First Fall

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>Vitamin D</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls</td>
<td>HR, 1.16</td>
<td>HR, 1.0</td>
</tr>
<tr>
<td>Fractures</td>
<td>(95% CI, 1.05-1.29)</td>
<td>(95% CI, 0.99-1.59)</td>
</tr>
</tbody>
</table>

Mortality (All-cause, Cancer, CVD)

The Uppsala Longitudinal Study of Adult Men, a community based cohort
(age at baseline: 71 y; n = 1194; 12.7 yr follow up)
What should we be doing with vitamin D supplementation?

<table>
<thead>
<tr>
<th>Life Stage Group (years)</th>
<th>Vitamin D Intake (IU/day)</th>
<th>Serum 25OHD Levels (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diet Alone&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Total Intake&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>288 ± 8</td>
<td>364 ± 16</td>
</tr>
<tr>
<td>4–8</td>
<td>256 ± 12</td>
<td>372 ± 16</td>
</tr>
<tr>
<td>9–13</td>
<td>228 ± 8</td>
<td>300 ± 28</td>
</tr>
<tr>
<td>14–18</td>
<td>244 ± 16</td>
<td>376 ± 20</td>
</tr>
<tr>
<td>19–30</td>
<td>204 ± 12</td>
<td>264 ± 16</td>
</tr>
<tr>
<td>31–50</td>
<td>216 ± 12</td>
<td>316 ± 12</td>
</tr>
<tr>
<td>51–70</td>
<td>204 ± 12</td>
<td>352 ± 16</td>
</tr>
<tr>
<td>71+</td>
<td>224 ± 16</td>
<td>428 ± 28</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>276 ± 16</td>
<td>336 ± 16</td>
</tr>
<tr>
<td>4–8</td>
<td>220 ± 12</td>
<td>316 ± 24</td>
</tr>
<tr>
<td>9–13</td>
<td>212 ± 24</td>
<td>308 ± 40</td>
</tr>
<tr>
<td>14–18</td>
<td>152 ± 8</td>
<td>200 ± 20</td>
</tr>
<tr>
<td>19–30</td>
<td>144 ± 12</td>
<td>212 ± 12</td>
</tr>
<tr>
<td>31–50</td>
<td>176 ± 12</td>
<td>308 ± 20</td>
</tr>
<tr>
<td>51–70</td>
<td>156 ± 16</td>
<td>404 ± 40</td>
</tr>
<tr>
<td>71+</td>
<td>180 ± 8</td>
<td>400 ± 20</td>
</tr>
</tbody>
</table>

NOTE: IU = International Units; SE = standard error.
<sup>1</sup>Data are mean ± SE for foods only.
<sup>2</sup>Data are mean ± SE for total intake: foods and dietary supplements.
<sup>3</sup>Data are mean ± SE.

Extended Oral Dosing of Vitamin D

Heaney 2010

Simulated Dose-Response of Total Dietary Vitamin D Intake and Achieved 25OHD at Latitudes >50° During Winter
Vitamin D upcoming trials

<table>
<thead>
<tr>
<th>Name</th>
<th>Place</th>
<th>Participants</th>
<th>Dose</th>
<th>Main Outcomes</th>
<th>Current State</th>
<th>Results Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>VITAL</td>
<td>U.S.</td>
<td>20,000, men: 50+, women: 55+</td>
<td>2000 IU D$_3$ daily</td>
<td>Cancer, Cardiovascular disease</td>
<td>Recruitment to finish end of 2012</td>
<td>2017</td>
</tr>
<tr>
<td>FIND</td>
<td>Finland</td>
<td>18,000, men: 60+, women: 65+</td>
<td>1600 IU D$_3$, daily or 3200 IU D$_3$, daily</td>
<td>Cancer, Cardiovascular disease, Diabetes</td>
<td>Recruitment started in spring, supplementation to start in autumn</td>
<td>2020</td>
</tr>
<tr>
<td>VIDA</td>
<td>New Zealand</td>
<td>5100, 50+</td>
<td>100,000 IU D$_3$, a month (300,000 IU in June)</td>
<td>Cardiovascular disease, Respiratory disease, Fractures</td>
<td>Recruitment to finish this year</td>
<td>2017</td>
</tr>
<tr>
<td>DOHealth</td>
<td>European cities</td>
<td>2150, 70+</td>
<td>2000 IU D$_3$, daily</td>
<td>Infections, Fractures, Blood pressure, Cognitive function, Lower extremity function</td>
<td>Recruiting</td>
<td>2017</td>
</tr>
<tr>
<td>VIDAL</td>
<td>U.K.</td>
<td>20,000, 65-84</td>
<td>60,000 IU monthly</td>
<td>Longevity and others</td>
<td>Planned 2-year feasibility study on 1600 patients is recruiting</td>
<td>2020 (if main study gets go-ahead)</td>
</tr>
</tbody>
</table>
Take Home Messages

• Vitamin D is a hormone that promotes calcium absorption in the gut
• Impaired calcium absorption due to low vitamin D reduces mineralization and leads to changes in bone microstructure
• There is minimal RPCT data to support vitamin D supplementation to prevent any chronic disease-except in the frail with OM
• Basic studies of vitamin D are essential to fully understand its actions
VDR null mice have increased energy expenditure

Figure 2. Body fat percentage and morphology of white adipose tissue (WAT) and brown adipose tissue (BAT). A and B: body fat percentage of male (♂) and female (♀) WT and VDR(+/-) mice on the HCA diet or HF diet. *p < 0.05 and **p < 0.005 vs. WT, n = 4-11 in each genotype. C and D: hematoxylin and eosin (H&E) staining of WAT (C) or BAT (D) from WT and VDR(+/-) mice on the HF diet. E and F: RT-PCR examination of vitamin D receptor (VDR) expression in WAT (E) and BAT (F). C, negative control; Kd, kidney; M, molecular weight marker.

Targeted Expression of Human Vitamin D Receptor in Adipocytes Decreases Energy Expenditure and Induces Obesity in Mice

Karl E. Wong, Juan Kong, Wenshuo Zhang, Frances L. Szeto, Honggang Ye, Dillip K. Deb, Matthew J. Brady, and Yan Chun Li

From the *Committee on Molecular Metabolism and Nutrition and **Department of Medicine, Division of Biological Sciences, The University of Chicago, Chicago, Illinois 60637

Figure 9. Lipolysis in WAT. A: real-time RT-PCR quantitation of rate-limiting enzymes in lipolysis, ATGL, and HSL, in the WAT from WT and Tg mice (n = 7-9 per genotype). B: in vitro lipolysis assay. WAT isolated from WT or Tg mice was not treated (WT) or treated with isoproterenol (ISO) for 1 h before determining the amount of glycerol released from WAT into the medium. *p < 0.05 versus WT, n = 3 per genotype. C: suppression of ATGL and HSL by 1,25-dihydroxyvitamin D(3) (1,25VD) in NIH 3T3-L1 adipocytes. Differentiated 3T3-L1 cells were treated with ethanol (DMSO) vehicle or 20 nm 1,25-dihydroxyvitamin D overnight, and ATGL and HSL mRNA levels were quantified by real-time RT-PCR. *p < 0.05 versus ETCH.