Vitamin D: What’s New and Not?

Clifford J Rosen MD
Maine Medical Center Research Institute
rosenc@mmc.org

Conflict of Interest Statement - Corporate

• NO STOCKS or EQUITY
• Editor- UpToDate, New England Journal of Medicine, and Endocrine Reviews
• Laboratory Support:
  – Alexion Pharmaceuticals- Hypophosphatasia
• Speakers bureaus
  – None
  – no consulting fees

Outline

• The Vitamin D paradox-the Ugly!!!
  – Little evidence, widespread usage

• Vitamin D: Bone- the Good and Bad
  – 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.

1927

1980

US$40 MILLION

2005

US$50 MILLION

2015

US$425 MILLION

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

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

If there is, maybe this is MAGICAL THINKING

Vitamin D and Implications for Health
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.

**Summary-Part I**

- 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.
- It is unresolved whether 25OHD is really low in AA.

**Does DBP concentration vary by ethnicity?**

<table>
<thead>
<tr>
<th>Study</th>
<th>Black</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al, 2014</td>
<td>152 ± 107</td>
<td>301 ± 210</td>
</tr>
<tr>
<td>Powe et al, 2013</td>
<td>168 ± 3</td>
<td>337 ± 5</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</td>
<td>248 ± 122</td>
</tr>
<tr>
<td>Winters et al, 2009</td>
<td>491 ± 128</td>
<td>529 ± 202</td>
</tr>
<tr>
<td>Bouillon et al, 1977</td>
<td>329 ± 54</td>
<td>329 ± 43</td>
</tr>
</tbody>
</table>

- African Americans
- White Americans

*No ethnic difference (P<0.05)**
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

A Closer Look at the Randomized Controlled Trials

The NEW ENGLAND JOURNAL of MEDICINE

Calcium plus Vitamin D Supplementation and the Risk of Fractures

Calcium supplementation X100 mg/day — no. (%) 5,192 (98.4) 5,313 (98.3)
Total calcium intake (supplements, diet, and medications)
Mean — mg/day 318.9±54 315.4±58
<500 mg/day — no. (%) 5,108 (98.6) 5,089 (98.2)
500 to 1200 mg/day — no. (%) 4,715 (92.5) 4,665 (92.7)
>1200 mg/day — no. (%) 7,092 (13.5) 7,895 (13.9)
Total calcium intake (supplements and diet)
Mean — IU/day 315±26 368±26
<100 IU/day 6,827 (98.6) 6,476 (98.6)
100 to <400 IU/day 3,575 (98.6) 3,423 (98.5)
400 to <800 IU/day 4,188 (98.6) 4,293 (98.7)
>800 IU/day 1,427 (98.6) 1,504 (98.6)

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>Rate of fracture — no. of cases (annualized %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>179 (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>2,102 (1.64)</td>
<td>2,154 (1.76)</td>
<td>0.96 (0.91–1.02)</td>
</tr>
<tr>
<td>Rate of fracture — no. of cases (annualized %)</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>Analysis excluding follow-up time for participants 6 mo after nonadherence detected</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>1,119 (1.83)</td>
<td>1,222 (1.72)</td>
<td>0.94 (0.87–1.02)</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
Why Might Vitamin D Supplementation Protect Against Fractures in the Elderly?

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.
AHRQ Evidence Report, 2014

“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 and insulin action

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

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

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

Studies reviewed by Atkin et al. [JUIN 2011]
Effect of Vitamin D₃ Supplementation (2,000 IU/day) on Disposition Index (beta-cell function) and HbA₁c

In participants at-risk-for-diabetes

So what's wrong with taking more vitamin D?

Table 1. Baseline Characteristics of Participants

<table>
<thead>
<tr>
<th>Age, median (IQR), y</th>
<th>Vitamin D (n = 1131)</th>
<th>Placebo (n = 1135)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>76.0 (73.0-80.0)</td>
<td>76.1 (73.0-80.0)</td>
</tr>
<tr>
<td>Baseline risk profile reported by participant (%) or physician-reported/high risk of falling</td>
<td>449 (39.7)</td>
<td>479 (41.5)</td>
</tr>
<tr>
<td>Uncontrolled diabetes since age 50 (%)</td>
<td>284 (25.4)</td>
<td>342 (29.7)</td>
</tr>
<tr>
<td>Malignant disease or history of cancer (%)</td>
<td>96 (10.6)</td>
<td>100 (10.5)</td>
</tr>
<tr>
<td>Lower extremity mobility</td>
<td>240 (21.4)</td>
<td>275 (24.6)</td>
</tr>
<tr>
<td>Early calcium intake, mg²</td>
<td>352 (29)</td>
<td>352 (29)</td>
</tr>
<tr>
<td>800-1200</td>
<td>316 (26)</td>
<td>363 (25)</td>
</tr>
<tr>
<td>1200-1500</td>
<td>158 (13)</td>
<td>186 (16)</td>
</tr>
<tr>
<td>&gt;1500</td>
<td>775 (66)</td>
<td>796 (67)</td>
</tr>
<tr>
<td>Biochemical measures, median (IQR)</td>
<td>50 (40-65)</td>
<td>45 (40-67)</td>
</tr>
<tr>
<td>25-hydroxycholecalciferol, nmol/L</td>
<td>5.2 (4.2-7.0)</td>
<td>5.0 (4.2-7.0)</td>
</tr>
</tbody>
</table>

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

Sanders et al., 2010
What should we be doing with vitamin D supplementation?
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

Baseline, 6-mo, and final serum 25OHDL levels are presented according to dosage of vitamin D or placebo. A quadratic curve was the best fit for each dosage group, the placebo group compared with all vitamin D dose groups individually (p < 0.05). 25(OH)D3 < 25-hydroxyvitamin D.
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, high risk of falls, or low 25OHD
• Basic studies of vitamin D are essential to fully understand its actions

Conflicts of Interest
- II

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