Vitamin D and Calcium Therapy:
how much is enough

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DISCLOSURE

Nothing to disclose

RECOMMENDATIONS FROM THE INSTITUTE OF MEDICINE

25OHD level of 20ng/ml is enough (UL 50ng/ml)
600 IU/qd is enough (800 IU qd for >71yo) (UL 4000IU qd)
Calcium intake during puberty: 1300 mg qd (UL 3000 mg qd)
Calcium intake ages 19-50: 1000mg qd (UL 2500 mg qd)
Calcium intake ages 51-70 males: 1000mg qd (UL 2000 mg qd)
Calcium intake ages 51-70 females: 1200mg qd (UL 2000 mg qd)
Calcium intake ages >70: 1200mg qd (UL 2000 mg qd)

But Controversy Reigns

The Endocrine Society Guidelines

25OHD level of 30ng/ml
1500-2000IU Vitamin D qd
Calcium recommendations comparable to IOM
Much of our data comes from epidemiologic studies

- Associations do not prove causality
- We do not know the optimal dose of vitamin D and calcium or the optimal level of 25OHD for most diseases for which it is used
- Too much of a good thing may be a bad thing
- We need RCTs of sufficient power and duration to answer these questions

The Calcium Controversy

Is Calcium Supplementation associated with cardiovascular events and myocardial infarction?

Metaanalysis suggesting calcium is hazardous to your health.

Random effects models of effect of calcium supplementation on cardiovascular events and death.
But Maybe Not
The Effects of Calcium Supplementation on Verified Coronary Heart Disease Hospitalization and Death in Postmenopausal Women: A Collaborative Meta-Analysis of Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Calcium</th>
<th>Placebo</th>
<th>Risk Ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Grant 2005 (Ca)</td>
<td>39</td>
<td>1113</td>
<td>31 1128</td>
</tr>
<tr>
<td>Jackson 2006</td>
<td>1405</td>
<td>18176</td>
<td>1263 18106</td>
</tr>
<tr>
<td>Larsen 2004</td>
<td>166</td>
<td>2983</td>
<td>169 2788</td>
</tr>
<tr>
<td>Prince 2006</td>
<td>64</td>
<td>769</td>
<td>60 730</td>
</tr>
<tr>
<td>Sandvik 2006</td>
<td>7</td>
<td>139</td>
<td>8 268</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>24284</td>
<td>24176</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.00, CHI^2 = 3.19, df = 5 (P = 0.67), P = 0.0%
Test for overall effect: Z = 0.68 (P = 0.51)

Favours calcium Favours placebo

How much calcium do we need?
Relation between calcium output (fecal calcium + urinary calcium excretion) and calcium intake

What About Vitamin D?
THE BIKLE APPROACH TO THE LITERATURE ON VITAMIN D THERAPY

- Rule 1: Someone somewhere has found an association between low vitamin D levels and every disease: clinical potential may be limitless
- Rule 2: If someone finds a disease with no association to low vitamin D levels, see rule 1

VITAMIN D DEFICIENCY WITH AGING

- Decreased vitamin D production in the skin
- Decreased vitamin D intake in the diet
- Decreased vitamin D absorption by intestine
- Decreased 1,25D production by the kidney
- Decreased intestinal response to 1,25D

Vitamin D Production in the Skin of Elderly vs Young Adults Following Total Body UVR

Declining Ability to Respond to PTH re 1,25D Production with Age

Holick MF et al., Lancet 2:1104-1105, 1989
How do we judge vitamin D sufficiency?

25(OH)D & SERUM iPTH*

290 consecutive pts. on a general medical ward – MGH


How much vitamin D does it take to suppress PTH?

Depends on basal levels of 25OHD and calcium intake
Various levels of serum 25OHD (nanograms per milliliter) at which serum PTH (picograms per milliliter) plateaus and/or is maximally suppressed.

Sai A J et al. JCEM 2011;96:E436-E446

The relationship between PTH suppression and vitamin D depends on calcium intake


Response of PTH to Vitamin D Depends on Basal 25OHD Levels

How Much Vitamin D is Required to Stimulate Intestinal Calcium Absorption

Depends on basal levels of 25OHD
Modest increase in 12-month calcium absorption (percent absorbed) on vitamin D3 doses of 400–4800 IU daily in healthy adults.

How Much Vitamin D is Required for Skeletal Health?
Depends on basal vitamin D levels and calcium intake

Serum 25(OH)D and Hip BMD

- NHANES-III
- Adults Age 20 – 49 yrs
- LOWESS plot of slope of BMD on 25(OH)D


Lack of increase in BMD with vitamin D supplementation in D replete subjects


DD 40,000IU D per wk, DP 20,000IU D per wk, PP placebo; all on 500mg Ca/day

JCEM 2012;97:3550-3556

Gallagher J C et al. JCEM 2012;97:3550-3556
Increased osteoid at 25OHD < 50nM

Fragility and Falls Contribute to Fracture Risk
Vitamin D Helps But Doses Required are Moderate

Mobility decreases with decreasing 25OHD levels
Physical performance in 1234 older persons in relation to 25-OHD.

Fall prevention with high dose (700-1000 IU a day) and low dose (200-600 IU a day) of supplemental vitamin D

WHAT ABOUT NON CLASSIC ACTIONS OF VITAMIN D

• Prodifferentiation, Antiproliferation
• Regulation of Hormone Secretion
• Modulation of Immune Function

COLORECTAL CANCER

• Nurses’ Health Study
• ages 46–78
• nested case-control study
• 193 incident cases
• 25(OH)D measured twice, prior to diagnosis
• Feskanich et al., Cancer Epidemiol Biomarkers Prev 2004 13:1502–08

25(OH)D Quintiles (with medians*)

* ng/mL
### Epidemiologic Studies are Mixed

#### Table 1: Meta-analyses of human epidemiologic studies

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Author</th>
<th>n Studies/Analysis</th>
<th>Pooled Relative Risks (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Colorectal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ma et al.⁴</td>
<td>9</td>
<td>0.88 (0.8-0.96) Vit D Intake</td>
</tr>
<tr>
<td></td>
<td>Yin et al.⁵</td>
<td>10</td>
<td>0.82 (0.69-0.97) 250HD levels</td>
</tr>
<tr>
<td>B. Breast</td>
<td>Chen et al ⁶</td>
<td>11</td>
<td>0.91 (0.85-0.97) Vit D intake</td>
</tr>
<tr>
<td></td>
<td>Gandini et al⁷</td>
<td>8</td>
<td>0.85 (0.78-0.92) 250HD levels</td>
</tr>
<tr>
<td></td>
<td>Gandini et al⁷</td>
<td>10</td>
<td>0.87 (0.72-1.06) prospective [5]</td>
</tr>
<tr>
<td>C. Prostate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gandini et al⁸</td>
<td>11</td>
<td>0.99 (0.95-1.03) 250HD levels</td>
</tr>
<tr>
<td></td>
<td>Gilbert et al⁹</td>
<td>13</td>
<td>1.14 (1.09-1.19) Vit D intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.04 (1.00-1.10) 250HD levels</td>
</tr>
</tbody>
</table>

Bikle, Endocrine 46: 29-38, 2014

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#### Effect of calcium and vitamin D on progression to DM

- **500mg Ca + 700u D3**
- **placebo**


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#### Hormonal Regulation by and of 1,25(OH)₂D

- **Bone**
- **Kidney**
- **Parathyroid Glands**
- **Pancreas**
- **Insulin**
- **FGF23**
- **25 OHD**
- **ARN**
- **PTH**

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#### No clear benefit of vitamin D + calcium on BP

- **Study, Year (Reference)**
- **Scragg et al, 1995 (27)**
- **Pfeifer et al, 2001 (30)**
- **Sugden et al, 2008 (17)**
- **Jorde et al, 2009 (22)**
- **Krause et al, 1998 (33)**
- **Margolis et al, 2008 (32)**
- **Zittermann et al, 2009 (20)**
- **Schleithoff et al, 2006 (28)**
- **Nagpal et al, 2009 (29)**
- **Major et al, 2007 (31)**
- **All studies**
- **Excluding Margolis et al, 2008 (32)**
- **Low-dose vitamin D (≤1000 IU/d)**
- **High-dose vitamin D (≥1000 IU/d)**
- **Vitamin D alone**
- **Vitamin D and calcium**

- **Net Change in Systolic Blood Pressure**
  - From Baseline, mm Hg

Potential benefit for preventing MI

Table 3. Estimated Risks of MI by Level of 25(OH)D at Baseline During 10 Years of Follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>0-15.9</th>
<th>15.0-22.5</th>
<th>22.6-29.9</th>
<th>&gt;=30.0</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/events, No.</td>
<td>63/677</td>
<td>15/3237</td>
<td>185/2999</td>
<td>705/307</td>
<td>NA</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>2.42 (1.53-3.84)</td>
<td>1.55 (1.15-2.13)</td>
<td>1.72 (1.29-2.31)</td>
<td>1.95 (1.13-3.35)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>HR$^a$</td>
<td>2.01 (1.23-3.33)</td>
<td>1.45 (0.89-2.32)</td>
<td>1.75 (1.18-2.59)</td>
<td>1.95 (1.13-3.35)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>HR$^b$</td>
<td>2.09 (1.24-3.46)</td>
<td>1.43 (0.86-2.32)</td>
<td>1.66 (1.10-2.49)</td>
<td>1.95 (1.13-3.35)</td>
<td>1.00 (Reference)</td>
</tr>
</tbody>
</table>

Rejnmark L et al. JCEM 2012;97:2670-2681

Adaptive Immunity

Innate Immunity

**SUMMARY**

- Vitamin D and calcium deficiency is detrimental to health.
- The optimal levels of vitamin D intake and 25OHD levels in blood are not established with certainty and may vary with calcium intake and disease process.
- Megadoses of vitamin D are NOT indicated and may be detrimental.
- Calcium has an important synergistic role with vitamin D in maintaining health—calcium does not increase the risk of CVD or death.

**RECOMMENDATIONS**

- 800-2000 IU vitamin D per day is safe and generally sufficient to achieve a serum level of 25OHD around 30ng/ml. Higher levels have not been proven to be better.
- Rule of thumb: For repletion, supplement with 100IU vitamin D for each 1ng/ml increment of 25OHD desired.
- 800-1200mg calcium per day in adults should suffice to maintain balance in most individuals without malabsorption—urine calcium provides a good guide with a goal around 150mg/24hr.