The role of calcium and vitamin D in bone health in the general population

Bess Dawson-Hughes, M.D.
Risk Factors for Osteoporosis

**MODIFIABLE**
- Sedentary
- Poor diet – Ca, vit D
- Smoking
- Excess alcohol
- Early loss of estrogen
- Thinness

**NOT MODIFIABLE**
- Age
- Heredity
- Medications- e.g., steroids
- Prior hip or spine fx
Basis for Setting Calcium Intake RDA
(amount required for maximal calcium retention from balance studies)

Spencer H, 1984
Jackman L, 1997
Calcium Intake and Risk of Hip Fracture (in 61,433 Swedish Women in Mammography Cohort)

Calcium Supplementation and Hip Fracture Risk
(170,991 men and women, 2954 fractures)

Women
RR 1.01 [0.97, 1.05]

Men
RR 0.92 [0.82, 1.03]

Calcium Supplementation and Non-vertebral Fracture Risk in Men and Women

RR = 0.92 [0.81, 1.05]

Food vs supplemental calcium and stone risk
Results of Observational Study

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food Ca</td>
<td>&lt;488 mg</td>
<td>&gt;1098 mg</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>0.65*</td>
</tr>
</tbody>
</table>

| Supp Ca | 0 mg              | >500 mg |
|         | 1.0               | 1.21*  |

* P for trend < 0.05
Curran GC. Ann Int Med 1997;126:497
Safety of Ca Supplements
Kidney Stones in WHI

Wallace RB. AJCN 2011;doi 10.3945/ajcn.110.0023350.
Effect of Calcium Supplements on Risk of MI
(RCT: 45 events in 31 women vs 19 events in 14 women, P = 0.01)

Bolland MJ. BMJ 2010;341:c3691; doi:10.1136/bmj.c3691.
Effect of Calcium Supplements on Risk of MI

Bolland MJ. BMJ 2010;341:c391;doi:10.1136/bmj.c3691.
Ca supplement use is associated with increased risk of MI

- Heidelberg cohort: 23,980 adults aged 35-64 yrs followed for 11 years

- HR for Ca supplement use: 1.86 [1.17, 2.96]

Li K. Heart 2012; 98: 920-925.
Association of calcium intake with coronary artery calcification

Framingham Off-spring; mean age 60 yrs; 690 women (open bars) and 588 men (filled)

WHI ANALYSIS

• In the WHI study (n = 36282, randomized to receive 1000 mg Ca/400 IU D daily or placebo [mean baseline Ca intake ~1150 mg/d]), there was no effect of Ca/D on coronary or cerebrovascular events

• MI/CAD death HR = 1.04 (0.92-1.18); Stroke HR = 0.95 (0.82-1.10)

• In subgroup analyses, no interaction with higher total Ca intake at baseline

Ca Supplementation and Risk of Atherosclerotic Vascular Disease
5-yr RCT + 4 yr F/U in 1460 women, mean age 75 yr; 1200 mg/d Ca vs P

HR = 0.919, [0.737, 1.146]

Lewis JR. JBMR 2011;26:35-41.
## Calcium RDA
**IOM 2011**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 51-70</td>
<td>1000 mg/d</td>
<td>Age 51-70</td>
</tr>
<tr>
<td>Age 71+</td>
<td>1200 mg/d</td>
<td>Age 71+</td>
</tr>
</tbody>
</table>
Calcium Intake in the United States: Food Sources Only

Dietary Reference Intakes. IOM 2011.
Calcium recommendations

• Goal: RDA (1000-1200 mg/d)
• Food sources – first choice
• Use supplements to bring TOTAL intake to 1000 to 1200 mg
• Rarely is more than 500 to 600 mg of supplemental calcium needed
Vitamin D Insufficiency

- Ca absorption
- PTH
- Bone TO and loss
- Fractures

- Muscle mass
- Muscle strength
- Falls
NHANES III – Serum 25(OH)D and Performance

Walk time

Sit-to-stand

Effect of Vitamin D$_3$ on Falls

(124 nursing home residents, mean age 89 years, 5 mo follow-up)

Achieved 25(OH)D serum concentration in treatment group (nmol/l)

Vitamin D and Falls
(RCT in 173 acute hip fracture patients
800 vs 2000 IU/d for 1 yr)

• Doses and 25OHD levels:
  800 IU group (39 → 88 nmol/L)
  2000 IU group (39 → 112 nmol/L)

• Outcome:
  No difference in first fallers or number of falls in the two dose groups

Effect of High Dose Vitamin D on Falls and Fractures in 2,256 Women age 70+ (500,000 IU orally once per year)

Sanders KM. JAMA 2010;303:1815-1822.
• 25OHD levels of 65 – 90 nmol/L (26 – 36 ng/ml) are associated with a 15-20% decrease in risk of falling.

• Increasing 25OHD levels above this range doesn’t appear to add benefit.

• High annual doses of vitamin D increase risk of falling.
Serum PTH and 25(OH)D Vary Inversely

(387 healthy men and women age 65 years and older)

Vitamin D Supplementation and Bone Mineral Density
Meta-analysis of 23 RCTs

Reid I. Lancet 2013; doi.org/10.1016/S0140-6736(13)61647-5.
Impact of Vitamin D and Calcium on Femoral Neck BMD in Men age 65+

Vitamin D and fracture prevention
Individual Subject Level Meta-analysis of RCTs

- 31,022 persons, 91% women, 11 RCTs
- Mean age 76 years (all age 65+)
- 1111 hip fxs, 3770 non-vertebral fxs
- Actual D intake (personal supplements, study pills x compliance)

Intent-to-Treat Analysis

• Hip fracture           RR  0.90 [0.80-1.01]

• Non-vert fracture     RR  0.93 [0.87-0.99]

Risk of Fracture by quartile of vitamin D intake

Meta-analysis of individuals from RCTs
(31,022 persons, mean age 76 yrs)

Effect of vitamin D as a function of age, dwelling and calcium supplement use

Spinal bone loss over 1-2 yr in women with breast cancer taking calcium and vitamin D

Premenopausal women

Postmenopausal women

Role of calcium and vitamin D in patients on pharmacotherapy for osteoporosis
# Fracture Prevention Trials: Calcium and Vitamin D Use and Results

<table>
<thead>
<tr>
<th>Drug/Study</th>
<th>Ca, mg/d</th>
<th>Vit D, IU/d</th>
<th>Fracture risk reduction (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liberman ‘95</td>
<td>500</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Black ‘96</td>
<td>500*</td>
<td>250</td>
<td>0.5</td>
</tr>
<tr>
<td>Cummings ‘98</td>
<td>500*</td>
<td>250</td>
<td>0.6</td>
</tr>
<tr>
<td>Risedronate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harris ‘99</td>
<td>1,000</td>
<td>500†</td>
<td>0.6</td>
</tr>
<tr>
<td>Raloxifene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ettinger ‘99</td>
<td>500</td>
<td>400-600</td>
<td>0.7</td>
</tr>
</tbody>
</table>

* If dietary calcium < 1,000 mg  † If 25(OH)D level < 40 nmol/L
<table>
<thead>
<tr>
<th>Age / EAR/RDA</th>
<th>D intake IU/d</th>
<th>Target 25OHD, nmol/L</th>
<th>Functional indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>51-70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EAR</td>
<td>400</td>
<td>40</td>
<td>Bone health</td>
</tr>
<tr>
<td>RDA</td>
<td>600</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>71+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EAR</td>
<td>400</td>
<td>40</td>
<td>Fractures</td>
</tr>
<tr>
<td>RDA</td>
<td>800</td>
<td>50</td>
<td></td>
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</table>
IOF Position Statement
Vitamin D Recommendations for Older Adults

- Adults with little regular sun exposure should take 800 to 1000 IU/d of vitamin D3.

- At risk groups for deficiency should have 25OHD measured and be supplemented in amounts needed to reach serum 25OHD level of 75 nmol/l.

Individuals at Increased Risk for Low 25OHD Levels

- Osteoporosis
- Obese
- Little sun exposure
- Dark skin
- High latitude
- Sunscreen use
- Malabsorption
- Anti-epileptics (increase metabolism)
To Increase serum 25OHD with vitamin D:

- 1 mcg ➞ 0.7 to 1.1 nmol/L ↑
- 100 IU ➞ 0.7 to 1.1 ng/ml ↑
Serum 25(OH)D Responses to 1000 (A) and 4000 (B) IU/d of Vitamin D₃

Effects of the same cumulative dose of vitamin D₃, equivalent to 1500 IU/d, but given once daily, once weekly, or once monthly, on serum 25(OH)D

Impact of vitamin D2 and D3 on serum 25OHD
1600 IU daily (left) and 50,000 IU monthly (right)

Binkley N. JCEM 2011;96:981-988
Conclusions - Calcium

• A total calcium intake of 1000 to 1200 is sufficient for bone health and more isn’t ‘better’.

• Exceeding this amount through supplement use may increase risk of kidney stones and possibly CV disease.

• There is no suggestion that calcium from food sources is risky.

• Therefore meeting the calcium requirement through diet is recommended.
Conclusions – Vitamin D

• A mean intake of 800 IU per day (resulting in a 25OHD level of 65-90 nmol/L) lowers risk of falling by about 20% in older adults. Higher doses do not provide additional benefit.

• A mean intake of $\geq 800$ IU per day (resulting a 25OHD level $> 60$ nmol/L) lowers hip fracture risk by up to 30% and non-vertebral fracture risk by 14% in both general and high risk older populations. High annual oral doses increase risk of falls and fractures.

• High risk patients should have 25OHD measured and doses titrated as needed to reach target; others should be supplemented with 800 to 1000 IU of D3 per day.
Conclusions (3)

• Calcium and vitamin D alone have not been tested in cancer patients, but observational studies reveal that they are not sufficient to prevent bone loss in breast cancer patients and others with gonadal insufficiency.
• However, they are essential components of any regimen to prevent bone loss in these patients.
Bolland reanalysis of WHI

**Hypothesis:** “Ca supplement use may obscure adverse effect of Ca on CVD”

<table>
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<tr>
<th></th>
<th>No personal Ca use</th>
<th>Any personal Ca use</th>
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</thead>
<tbody>
<tr>
<td>CaD</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Baseline MI rate, %</td>
<td>2.3</td>
<td>2.0</td>
</tr>
<tr>
<td>HR</td>
<td>1.20 [0.99, 1.47]</td>
<td>0.94 [0.77, 1.114]</td>
</tr>
</tbody>
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Effect of Exercise on Bone Density


Effect of Tai Chi on Risk of Falling
Home-based program, 15 min/d for 15 wks in 200 men and women age 70+

Calcium and Vitamin D Intakes and Serum PTH

Icelandic population, males (58 ± 14 yrs) and females (54 ± 16 yrs)

Steingrimsdottir L, JAMA 2005; 294:2336-2341
Relative importance of 25(OH)D status and calcium intake with respect to hip BMD (n=4958)

P-value for trend across categories of 25(OH)D levels: < 0.0001

Adjustments: calcium intake, age, race/ethnicity, body mass index, height, total calorie intake, estrogen use among women, physical activity, smoking, and socio-economic status.

## Vitamin D Content of Foods

<table>
<thead>
<tr>
<th>Food</th>
<th>mcg</th>
<th>IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon (3.5 oz)</td>
<td>9</td>
<td>360</td>
</tr>
<tr>
<td>Tuna (3.5)</td>
<td>5</td>
<td>200</td>
</tr>
<tr>
<td>Egg (1)</td>
<td>0.5</td>
<td>20</td>
</tr>
<tr>
<td>Liver (3.5 oz)</td>
<td>0.4</td>
<td>16</td>
</tr>
</tbody>
</table>

Ref: USDA database.
Forbes, 1979
Effect of Estrogen ± Calcium on BMD
(Meta-analysis of 31 estrogen trials)

<table>
<thead>
<tr>
<th></th>
<th>Estrogen Alone</th>
<th>Estrogen + Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of trials</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Years since menopause</td>
<td>3 ± 1</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>Calcium intake, mg</td>
<td>589 ± 37</td>
<td>1,183 ± 65</td>
</tr>
</tbody>
</table>

Effect of Estrogen ± Calcium on Change in BMD

Calcitonin, Calcium and Vertebral Fracture Risk – MEDOS Study


*P=0.01
Vitamin D - Clinical Considerations

- Who is at risk for low 25OHD?
- Who should be measured?
- Supplementing to target level
- Dosing frequency
- D2 vs D3
Calcium Supplementation for the Prevention of Postmenopausal Bone Loss: a meta-analysis

(Weighted mean difference for lumbar spine after treatment with calcium at 2 yr)