CLINICAL UPDATE:
Where Are We Now With Vitamin D?

Terry Aspray, Bone Clinic Freeman Hospital
and
Institute of Cellular Medicine, Newcastle University
Newcastle upon Tyne
Outline

• Sources of vitamin D
• Risks of deficiency
  – Bone
    • Fractures
  – Muscle
    • Falls
• Treatment
  – Benefits
  – Risks?

– Other putative roles
  (not for this presentation)
  • Immunity modulation
  • Cancer prevention
  • Multiple sclerosis
  • Cardiovascular risk

RICKETS

VITAMIN D DEFICIENCY
DM, MS, RA, INFECTIONS
HBP, CHD, CANCER
## Guidelines: Recent History

<table>
<thead>
<tr>
<th>Date</th>
<th>Who</th>
<th>Region</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Institute of Medicine</td>
<td>North America</td>
<td>Dietary Reference Intakes for Calcium &amp; Vitamin D</td>
</tr>
<tr>
<td>2011</td>
<td>Endocrine Society</td>
<td>North America</td>
<td>Evaluation, Treatment, &amp; Prevention of Vitamin D Deficiency</td>
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<tr>
<td>2012</td>
<td>European Food Safety Authority</td>
<td>Europe</td>
<td>Scientific Opinion on the Tolerable Upper Intake Level of vitamin D</td>
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<tr>
<td>2013</td>
<td>National Osteoporosis Society</td>
<td>UK</td>
<td>Vitamin D &amp; bone health: a practical clinical guideline for patient management</td>
</tr>
<tr>
<td>2014</td>
<td>Preventive Services Task Force</td>
<td>USA</td>
<td>(USPSTF) Final Recommendation Statement: Vitamin D Deficiency</td>
</tr>
<tr>
<td>2015</td>
<td>National Institute for Health &amp; Care Excellence</td>
<td>England, Wales &amp; N.I.</td>
<td>NICE PH56- Vitamin D: increasing supplement use among at-risk groups</td>
</tr>
<tr>
<td>2015</td>
<td>Scientific Advisory Committee on Nutrition</td>
<td>UK</td>
<td>Draft SACN Vitamin D &amp; Health report</td>
</tr>
</tbody>
</table>
Case

- 37 yr old Iranian woman
  - Rheumatology clinic
    - Whole body aches & pains
    - No symptoms/signs of joint inflammation
  - Diagnosis?

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Unit</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca(^{++})(corr)</td>
<td>1.98</td>
<td>mmol/L</td>
<td>2.2-2.6</td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.8</td>
<td>mmol/L</td>
<td>0.8-1.4</td>
</tr>
<tr>
<td>Creatinine</td>
<td>75</td>
<td>μmol/L</td>
<td>75-145</td>
</tr>
<tr>
<td>ALP</td>
<td>260</td>
<td></td>
<td>&lt;120</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>12</td>
<td>nmol/L</td>
<td></td>
</tr>
<tr>
<td>PTH</td>
<td>14</td>
<td>pmol/L</td>
<td>&lt;6.1</td>
</tr>
</tbody>
</table>
Where do we get vitamin D?

- **Sun:** UV B radiation causes 7-dehydrocholesterol to be converted into vitamin D₃ in the skin (80-90% of total vitamin D).
- **Diet:** Vitamin D₂ and vitamin D₃ (10-20% of total vitamin D).
- **Liver:** 25(OH)₂ vitamin D₂/D₃ is converted into 25-hydroxyvitamin D₂/D₃ through a process called 25 hydroxylation.
- **Kidney:** 1,25(OH)₂ vitamin D₂/D₃ (1α hydroxylation) is produced in the kidney, which regulates calcium homeostasis and bone metabolism.

**Classical actions:**
- Calcium homeostasis
- Bone metabolism
- Neuromuscular function
Where do we get vitamin D?

- **Sunlight**
  - Winter/Spring
    - No synthesis
    - Seasonal variation
      - 20-40nmol/L

- **North/South/Ethnic divide**
  - Surrey White ■
  - Aberdeen □
  - Surrey Asian ▲

MacDonald HM (2010)
Where do we get vitamin D?

• **Diet**
  - Oily fish (200-600IU)/100g
    - Sardines, tuna, salmon, mackerel
  - Cod liver oil (450IU)/tsp
    - Many are less potent...
  - Egg-yolk (60IU)
  - Fortification- UK (c.40IU)
    - Margarine
    - Milk (processed & powdered)
    - Breakfast cereals
      - (40-160IU)
Risks of deficiency: Osteomalacia (& Rickets)

- Case reports
  - 25(OH)D levels of 4-20 nmol/L
- Larger series*
  - mean 25(OH)D
    - 7.5 to 15 nmol/L

* SACN Draft report (2015)

- 87 yr old woman
  - Day hospital
    - Lives alone
    - Whole body aches & pains
    - Poor mobility

- Diagnosis?
Vitamin D and Muscle Strength

• Younger adults:
  – Six RCTs n=310
  – UL strength +0.32 SD
  – LL strength 0.32 SD

• Older adults:
  – 17 RCTs n=5,072
  – No effect
    • One study n=46: improved hip strength

Stockton et al Osteoporosis International (2011)

Hyperparathyroidism

- ↓25OHD & ↑PTH shows a plateau
- Vitamin D supplement leads to ↓PTH


MacDonald HM et al (2013) *JBMR*
Bone Mineral Density: Supplementation

**No** ↑BMD at LS or Total Hip

**↑BMD at Neck of Femur**

### A

<table>
<thead>
<tr>
<th>Study</th>
<th>Weighted mean difference in lumbar spine BMD (%) (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dawson-Hughes, 1991</td>
<td>0.7 (0.0 to 1.4)</td>
<td>12</td>
</tr>
<tr>
<td>Dawson-Hughes, 1995</td>
<td>-0.2 (-1.0 to 0.6)</td>
<td>9</td>
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<tr>
<td>Tuppurainen, 1998</td>
<td>0.9 (-2.9 to 4.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>Komulainen, 1999</td>
<td>-0.7 (-6.9 to 2.3)</td>
<td>2</td>
</tr>
<tr>
<td>Komulainen, 1999</td>
<td>-0.1 (-1.4 to 1.2)</td>
<td>3</td>
</tr>
<tr>
<td>Hunter, 2000</td>
<td>-0.1 (-1.9 to 1.7)</td>
<td>2</td>
</tr>
<tr>
<td>Patel, 2001</td>
<td>-0.6 (-1.3 to 0.2)</td>
<td>10</td>
</tr>
<tr>
<td>Cooper, 2003</td>
<td>-0.2 (-1.7 to 1.4)</td>
<td>2</td>
</tr>
<tr>
<td>Hanwood, 2004</td>
<td>-1.4 (-3.3 to 0.5)</td>
<td>2</td>
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<tr>
<td>Aloia, 2005</td>
<td>-0.1 (-0.5 to 0.4)</td>
<td>23</td>
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<td>Andersen, 2008</td>
<td>0.6 (-0.6 to 1.9)</td>
<td>3</td>
</tr>
<tr>
<td>Islam, 2010</td>
<td>1.7 (-0.5 to 3.9)</td>
<td>1</td>
</tr>
<tr>
<td>Jorde 2010</td>
<td>0.1 (-0.7 to 0.8)</td>
<td>10</td>
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<tr>
<td>Grimnes, 2011</td>
<td>-0.1 (-0.8 to 0.7)</td>
<td>10</td>
</tr>
<tr>
<td>Rastelli, 2011</td>
<td>0.5 (-1.7 to 2.7)</td>
<td>1</td>
</tr>
<tr>
<td>Steffensen, 2011</td>
<td>-0.2 (-1.7 to 1.3)</td>
<td>2</td>
</tr>
<tr>
<td>Nieves, 2012</td>
<td>0.1 (-0.8 to 1.1)</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0.0 (-0.2 to 0.3)</td>
<td>p=0.8</td>
</tr>
</tbody>
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Test for heterogeneity:

\( I^2 = 0\% \), \( p = 0.6 \)

### B

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<td>Dawson-Hughes, 1995</td>
<td>1.5 (0.5 to 2.5)</td>
<td>10</td>
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<tr>
<td>Ooms, 1995</td>
<td>1.9 (0.4 to 3.4)</td>
<td>7</td>
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<tr>
<td>Tuppurainen, 1998</td>
<td>3.7 (-0.1 to 7.5)</td>
<td>2</td>
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<tr>
<td>Komulainen, 1999</td>
<td>0.1 (-1.2 to 1.4)</td>
<td>8</td>
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<td>Hanwood, 2004</td>
<td>1.1 (-1.1 to 3.2)</td>
<td>5</td>
</tr>
<tr>
<td>Islam, 2010</td>
<td>2.8 (1.5 to 4.1)</td>
<td>8</td>
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<td>Grimnes, 2011</td>
<td>-0.1 (-0.6 to 0.3)</td>
<td>12</td>
</tr>
<tr>
<td>Rastelli, 2011</td>
<td>1.8 (-0.1 to 3.8)</td>
<td>5</td>
</tr>
<tr>
<td>Nieves, 2012</td>
<td>0.6 (-0.1 to 1.3)</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0.8 (0.2 to 1.4)</td>
<td>p=0.005</td>
</tr>
</tbody>
</table>

Test for heterogeneity:

\( I^2 = 67\% \), \( p = 0.00027 \)

Meta-analysis (Reid (2014) Lancet)
Consequences of Vitamin D Deficiency

- **Osteomalacia & Rickets**
  - Classic presentation
  - Threshold of 25OHD?
    - 25nmol/L-SACN
    - 30nmol/L-IOM
    - 50nmol/L-Endo Soc
    - 75nmol/L-Priemel & others

- **Muscle weakness**
  - Classic presentation
  - Supplementation
    - Benefit in young adults
    - Less evident age 50+

- **Hyperparathyroidism**
  - Common in deficiency
  - Supplement ↓PTH

- **BMD**
  - Epidemiology
    - ↑BMD with ↑25OHD
  - Supplementation:
    - ↑BMD at NOF
    - No effect @ Total Hip/Spine
Clinical Outcomes: Fractures

- **Bischoff-Ferrari** (NEJM, 2012)
  - 31,022 subjects (>1,000 hip #)
  - Threshold for effect: 800iu/d?

- **Vitamin D without calcium**
  - Cochrane Review (Avenell 2014)
  - 11 trials, n=27,693
  - No effect: RR 1.12 (0.98 to 1.29)
Clinical Outcomes: Falls

- Bischoff-Ferrari (2009) BMJ
  - Vitamin D without calcium
  - High dose (>700IU/d) effective?
    - \( \downarrow \) falls by 19%

- Murad (2011) JCEM
  - 45,782: (n.b. less restricted criteria)
    - Vitamin D with calcium beneficial
    - Vitamin D monotherapy (NS)
    - Most benefit: trials of elderly women

\[\text{BGS Falls 2015}\]
Clinical evidence: vitamin D, falls & fracture prevention

- Treating rickets/osteomalacia
  - No argument!!

- Falls/Fractures: trials conflict
  - Dose of vitamin too low (in some)
  - With or without calcium
  - Dose effects

<table>
<thead>
<tr>
<th>Date</th>
<th>Who</th>
<th>Deficient (nmol/L)</th>
<th>Target (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>IOM</td>
<td>&lt;30</td>
<td>50</td>
</tr>
<tr>
<td>2011</td>
<td>Endo Soc</td>
<td>&lt;50</td>
<td>75+</td>
</tr>
<tr>
<td>2012</td>
<td>EFSA*</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2013</td>
<td>NOS</td>
<td>&lt;30</td>
<td>30 or 50</td>
</tr>
<tr>
<td>2015</td>
<td>SACN</td>
<td>&lt;25</td>
<td>≥25</td>
</tr>
</tbody>
</table>

Optimal blood 25OHD unclear for skeletal health...
1. Supplementation is needed to achieve this
2. Supplementation is relatively uncommon
4. Consider food fortification?

<table>
<thead>
<tr>
<th>Country</th>
<th>Age Group</th>
<th>Vitamin D Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK (2015)</td>
<td>Children &lt;4yrs</td>
<td>8.5-10 μg</td>
</tr>
<tr>
<td></td>
<td>Children &gt;4yrs</td>
<td>(RNI) 10 μg</td>
</tr>
<tr>
<td></td>
<td>Children &gt;4yrs</td>
<td>(RNI) 10 μg</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>10 μg</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>10 μg</td>
</tr>
</tbody>
</table>

| US (2010) | Children >1yrs | (EAR/RDA) 10/15 μg |
|          | Adult:         | μg |
|          | Age >70        | 10/20 μg |

25 ng = 1 I.U.
1 μg = 40 I.U.

Scientific Advisory Committee on Nutrition (SACN, draft 2015)
Ross et al. 2010 DRIs for Calcium and Vitamin D. Washington, USA
Giving Supplements: Fortified Foods

- **Meta-analysis** (n = 1513)
  - 14/16 studies: fortified foods
  - $\uparrow 440$ [120-1000] IU/d intake
  - $\uparrow 25OHD$ by 19.4 nmol/L
  - 1.2 nmol/L per 1μg ingested

“Safe & effective food-based strategies could increase serum 25OHD across the population ... with potential benefit for public health.”

Giving Supplements: Oral

Supplement
- 74 randomized trials
- 5 to 53.5 μg/d
- 200 to 21,400 IU/d
- vitamin D2 or D3
  e.g. D3, D2
  400IU: +28 +18 (nmol/L)
  800IU: +38 +28 (nmol/L)

Autier P et al. JCEM 2012;97:2606-2613

BGS Falls 2015
Vitamin D: Improve Compliance with Bolus Dosing?

No difference daily, weekly, monthly  
Daily more efficient than four-monthly

Ish-Shalon S. JCEM (2009)  
Pekkarinen T Clinical Endocrinology (2010)
High Dose Vitamin D?

- **300,000 IU**
  - Community oral D2, Smith (2007)
  - ↑ Hip fractures RR=1.49 (p=0.04)

- Care homes 10 mo i.m. D2, Law (2006)
  - ↑ Hip fractures (NS)

- **500,000 IU**
  - Oral D3 High risk annual, Sanders (2010)
  - For a median 3 yrs
  - First fall (NNH=10)
    - 73% placebo
    - 83% vitamin D
Risks of bolus dosing?

Bischoff Ferrari  Delft 2015

Aspray (unpublished) VDOP
Should We Give Calcium?

**Vitamin D**

**Hip Fracture**
- 11 trials, n=27,693
- No effect
- **RR 1.12 (0.98 to 1.29)**

**Ca/vitamin D**
- 9 trials, n=49,853
- Small Effect
  - RR 0.84 (0.74 to 0.96)
  - Especially care homes
  - RR 0.75 (0.62 to 0.92)

Cochrane Database of Systematic Reviews (2014)
Conclusions

Vitamin D
● RNI 400 iu/d
  ● difficult for many
  ● Lack of international agreement

● Benefits
  ● Treats Osteomalacia
  ● ↑Muscle strength in young
    ● not the old?
  ● ↓Falls: Dose >700IU/d?
  ● ↑BMD neck of femur
    ● No ↓fractures

● Concerns:
  ● High dose and falls (NNH=10)
    ● Even 2,000/d?
  ● High dose and fractures?

Vitamin D with Calcium
● ↓Fractures
  ● In frail/care homes
● ↓Falls
● ↓Mortality? (NNT=150)

Calcium and vitamin D supplementation?
● Assess requirements separately:
  ● Calcium 700mg/d
  ● Vitamin D 400iu (10 μg)/d

● Target supplementation
  ● ?Calcium/D3 1 tablet
  ● D3 monotherapy 1 caps