Discussion of Research Recommendations:
DRIs for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride

Dietary Reference Intake Research Synthesis Workshop
DRI Report on Calcium and Related Nutrients
Calcium - Research Recommendations

- Define impact of intake on mineral metabolism and peak bone mass
- Define genetic-intake interactions
- Define impact of intake in adults on skeletal and non-skeletal endpoints (e.g., blood pressure, cancer risk, diabetes)
- Define impact on renal stones
Calcium - Research Progress in Children

- Link between calcium intake and absorption is better defined, especially in adolescents
- Data now relate vitamin D polymorphisms and mineral metabolism
- Early milk consumption is now linked to reduced fracture risk in girls and in women
- Several calcium intervention trials; the longest revealed that girls who were taller at the end benefited from supplementation
- Racial differences in bone turnover and calcium metabolism have been described
Calcium – Research Progress in Adults

• Numerous randomized placebo controlled trials have been published; those with a low calcium placebo group and reasonable compliance have been positive
• DASH data link dairy foods to reduced blood pressure
• Several studies identify a small (3-5%) inverse effect of calcium on body weight
• Data on effect of high calcium intake on first kidney stone and on recurrence are now available
### Effect of Calcium (1200 mg) vs. Placebo on Fracture Risk

(1460 women, mean 75 years, Ca intake ~900 mg/d, 5-yr study)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>HR [95 CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>100%</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[0.67 - 1.12]</td>
</tr>
<tr>
<td>Adherent (80%)</td>
<td>57%</td>
<td>0.66</td>
</tr>
<tr>
<td>subjects</td>
<td></td>
<td>[0.45 – 0.97]</td>
</tr>
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</table>

Vitamin D – Research Recommendations

- Define optimal vitamin D intake for US/Canadian populations by age group, latitude and race
- Define relationship between intake and serum 25 (OH)D
- Influence of sunscreens
Define Optimal Vitamin D Intake

- Identify biological actions
- Define serum 25(OH)D needed to optimize function(s)
- Define relationship between intake and serum 25(OH)D level
Vitamin D – Biological Actions in Adults

• Musculoskeletal – PTH suppression, bone density, muscle performance, falls, fractures

• Other – diabetes, cancer, infection, periodontal disease, osteoarthritis
<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (IU/d)</th>
<th>25(OH)D (nmol/L)</th>
<th>ΔPTH (%)</th>
<th>Effect on non-vert fx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapuy</td>
<td>800</td>
<td>100</td>
<td>-47</td>
<td>+</td>
</tr>
<tr>
<td>Chapuy</td>
<td>800</td>
<td>100</td>
<td>-33</td>
<td>+</td>
</tr>
<tr>
<td>D-Hughes</td>
<td>700</td>
<td>112</td>
<td>-28</td>
<td>+</td>
</tr>
<tr>
<td>Trivedi</td>
<td>820</td>
<td>74</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Grant - RECORD</td>
<td>800</td>
<td>63(^a)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Jackson - WHI</td>
<td>400</td>
<td>59(^a)</td>
<td>?</td>
<td>NS</td>
</tr>
<tr>
<td>Lips</td>
<td>400</td>
<td>54</td>
<td>-6</td>
<td>NS</td>
</tr>
<tr>
<td>Meyer</td>
<td>400</td>
<td>64</td>
<td>?</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^a\) Estimates in subsets of subjects
Vitamin D Research Needs

- Children – define optimal 25 (OH)D for calcium metabolism and for bone accretion (greatest need is for ages 6 mo – 8 yrs)
- Adults – identify 25 (OH)D thresholds for non-skeletal endpoints
- Standardization of 25 (OH)D assays
- Better quantitation of the vitamin D content of foods
Phosphorus – Research Recommendations

- For ages 1-18, define intake needed to optimize bone accretion
- Define relationship between intake and blood level, for children and adults.
Phosphorus Research Remains A Priority

- Low intake – up to 15% of older women consume <70% of adequate intake
- Calcium supplement use - decreases bioavailability of dietary phosphorus
- Anabolic therapy for osteoporosis - higher demand

Magnesium – Research Recommendations

- Identify the Mg intake needed for maximal accretion (ages 1-18) and for preservation of bone (adults).

- Identify associations between Mg intake and the development of hypertension, cardiovascular disease, and diabetes.

- Identify and validate an accurate indicator of Mg status.
Magnesium – Research Progress

- Mg depletion studies have been done in rats.

- Several epidemiologic studies have found positive associations between magnesium intake and bone mass and negative associations with diabetes and stroke.
## Magnesium Depletion and the Skeleton in Rats

<table>
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<tr>
<th>Diet % Nutrient Requirement</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>↓ trabec vol, ↑osteoclast #</td>
</tr>
<tr>
<td>25&lt;sup&gt;b&lt;/sup&gt;</td>
<td>also ↑TNF-alpha</td>
</tr>
<tr>
<td>10&lt;sup&gt;c&lt;/sup&gt;</td>
<td>also ↑TNF-alpha</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Rude R. *OI* 2006; on-line.


Magnesium intake – associations with Diabetes and Stroke

**Diabetes**
In >100,000 subjects followed for 12 to 18 yrs:
High vs. low quintile       RR 0.66 [0.60 – 0.73]

**Stroke**
In 43,738 men followed for 8 yrs:
High vs. low quintile       RR 0.62 [0.43, 0.88]

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Research Progress – Indicators of Magnesium Status

- Indicators of Mg status have not progressed/changed

- 99% of body Mg is intracellular, of this 10-15% is in active free form

- Barbagallo and colleagues found no differences in intracellular $[\text{Mg}^{++}]$ in normals vs. hypertensives or normals vs. diabetics

Fluoride – Research Recommendations

• Epidemiologic research on habitual exposure to fluoride, effect on:
  – prevention of dental caries
  – quality of bone
  – risk of fluorosis

• Identify factors that influence fluoride absorption and retention (e.g., calcium intake, acid-base balance, altitude of residence)
Elevated fluoride concentrations – relationship to BMD and fractures

- 1300 women in 3 Iowa communities
- Four-year follow-up
- Outcomes – bone density and fracture

### Fluoride exposure, bone density and fractures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>High Ca</th>
<th>High Fluoride</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>368</td>
<td>406</td>
<td>526</td>
</tr>
<tr>
<td>Ca intake, mg</td>
<td>754</td>
<td>1001</td>
<td>679</td>
</tr>
<tr>
<td>F intake water, µmol/L</td>
<td>63.7</td>
<td>40.5</td>
<td>192.5</td>
</tr>
<tr>
<td>Serum F, µmol/L</td>
<td>1.60</td>
<td>1.22</td>
<td>2.11</td>
</tr>
<tr>
<td>BMD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>spine</td>
<td>1.179</td>
<td>1.197</td>
<td>1.195 (NS)</td>
</tr>
<tr>
<td>femoral neck</td>
<td>0.914</td>
<td>0.912</td>
<td>0.912 (NS)</td>
</tr>
<tr>
<td>dist radius</td>
<td>0.651</td>
<td>0.656</td>
<td>0.667 (p&lt;0.05)</td>
</tr>
<tr>
<td>Fractures, n</td>
<td>5</td>
<td>14</td>
<td>15</td>
</tr>
</tbody>
</table>

Fluoride and Prevention of Dental Caries

NHANES – Between 1988-94 and 1999-2002

- Caries in permanent teeth have declined
- Tooth loss in older adults has declined
- Prevalence of enamel fluorosis has increased (since 1980)
- Racial/ethnic disparities persist in caries and enamel fluorosis

“Optimally fluoridated water and fluoridated dentifrice are recommended for everyone but the use of other modalities (mouth rinses, supplements, gels, varnishes) should be used only in persons at high risk of caries.”