Beyond the ‘Big 5’ – Micronutrients of Emerging Interest for Public Health

Geoffry Smith
Essential Micronutrients Foundation
Singapore
geoff.smith@emfglobal.org
Micronutrient Deficiencies and Fortification – Beyond the Big 5

• Big 5 Success (Iodine) and not yet (Iron)
• Essential Micronutrients
  • Vitamin D
    • IOM and other recommendations
    • Bone health
    • SE Asia studies
    • Potential fortification
    • Non-skeletal functions of vitamin D

• Vitamin K (for Koagulation)
  • Chemistry and history
  • Phylloquinone
  • Menaquinone
  • Functions

• Further research
Micronutrient Deficiencies
– 100 years of discovery and progress

• Significant health impact
• Intakes may need to be and can be improved
• Strategies – Improved diet, supplementation, biofortification, food fortification
Micronutrient Deficiencies
– 100 years of discovery and progress

• The “discovery” of first vitamin often credited to the Polish-American biochemist Casimir Funk

• In 1912 he wrote of "... the deficient substances, which are of the nature of organic bases we will call “vitamines” [from “vital amines]; and we will speak of beri-beri or scurvy vitamine, which means a substance preventing the special disease”. (Journal of State Medicine, 1912, vol. 20, 341-354)

• Extract from rice polishing, based on work by Christiaan Eijkman in Jakarta (later Eijkman won Nobel Prize); and William Fletcher work in 1905 in KL (Lancet 1907) to prevent/cure beri-beri

• Thiamine (vitamin B1) was isolated in 1926 (in Java) and its chemical structure determined in 1936 (R.R. Williams – who had started his work in 1909 in Manila)

  » Early human experiments with pure crystals in Singapore in 1937
Micronutrient Deficiencies
– 100 years of discovery and progress

• Dr. W. Leonard Braddon - born in London, doctor in the Federated Malay States from 1888 to 1908. Much of his time was spent studying beri-beri. In 1907 he published his 544 page report “The Cause and Prevention of Beri-Beri” (summarized earlier in 1904)

> 1. In Individuals, according to the Writer’s Observations, this always happens.—In individuals it is the writer’s constant experience that the course of the disease is checked at once, in mild and subacute cases, merely upon changing the sort of rice eaten, without the application of any kind of ‘remedy,’ and without alteration in any other circumstances.

– William Fletcher work in 1905 in KL. (Rice and Beri-Beri, The Lancet, 1907)
– Carpenter, K., 2000, Beriberi, White Rice, and Vitamin B: A Disease, a Cause, and a Cure
Micronutrient Deficiencies – 100 years of discovery and progress

- The first vitamin to be named was vitamin A. The use of the letter A was the brainchild of the American biochemist Elmer McCollum (E.V. McCollum)
- He rejected Casimir Funk’s term ‘vitamine’ in favor of ‘Unidentified dietary factor fat-soluble A’ because the substance discovered by McCollum did not contain nitrogen
- Compromise proposed by Jack Drummond of University College, London, led to “vitamin” and letter designations for each (Biochem J, 1920, p.660)
## Micronutrient Deficiencies
- Human toll of vitamin and mineral deficiencies

<table>
<thead>
<tr>
<th>TYPE OF REPERCUSSION</th>
<th>NUMBERS AFFECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIVES LOST ANNUALLY</td>
<td>- 1.1 million children under five die due to vitamin A and zinc deficiencies</td>
</tr>
<tr>
<td></td>
<td>- 136,000 women and children die because of iron-deficiency anaemia</td>
</tr>
<tr>
<td>LIVES IMPAIRED ANNUALLY</td>
<td>- 18 million babies are born mentally impaired because of maternal iodine deficiency</td>
</tr>
<tr>
<td></td>
<td>- 150,000 babies are born with severe birth effects due to inadequate maternal folate intake</td>
</tr>
<tr>
<td></td>
<td>- 350,000 children become blind due to vitamin A deficiency</td>
</tr>
<tr>
<td>LOST PRODUCTIVITY</td>
<td>- 1.6 billion people suffer reduced productive capacity due to anaemia</td>
</tr>
</tbody>
</table>

UNICEF, 2009
Micronutrient Deficiencies – Global Iodine deficiency and excess

Iodine - success

• WHO recommended salt iodization as early as 1952
• As recently as 1990, only a handful of countries could demonstrate adequate iodine intake
• 1990 World Health Assembly agreed to action and UNICEF took up challenge
• Current data shows adequate iodine intakes in 112 countries, deficient in 30 countries (including industrialized countries)
• However, even mild deficiencies can lead to impaired cognitive development in offspring
Children of women with an iodine-to-creatinine ratio of less than 150 μg/g were more likely to have scores in the lowest quartile for verbal IQ, reading accuracy, and reading comprehension compared to mothers with ratios of 150 μg/g or more.

When the less than 150 μg/g group was subdivided, scores worsened at 50–150 μg/g, and further at less than 50 μg/g.
Micronutrient Deficiencies-Global

Anemia (pre-school children; not all caused by iron deficiency)

Iron deficiency – not so much progress

- Anemia often measured, not actual iron deficiency
- Infection affects common measurement (serum ferritin)
- Organoleptic issues – many iron compounds affect color and taste
- Bioavailability widely varies among iron compounds, and is greatly affected by iron absorption inhibitors (i.e., phytic acid)
- “Most current iron fortification programs are likely to be ineffective” (Hurrell, 2010, Food and Nutrition Bulletin, vol. 31, no. 1, pages S7-S21)
- Addressed by WHO/FAO/UNICEF guidelines, but so far mostly followed in some countries in Africa and Central Asia
# Challenges in fortification

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Flour Extraction Rate</th>
<th>Compound</th>
<th>Level of nutrient to be added in parts per million (ppm) by estimated average per capita wheat flour availability (g/day)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;75² g/day</td>
</tr>
<tr>
<td>Iron</td>
<td>Low</td>
<td>NaFeEDTA</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ferrous Sulfate</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ferrous Fumarate</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Electrolytic Iron</td>
<td>NR³</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>NaFeEDTA</td>
<td>40</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>Low or High</td>
<td>Folic Acid</td>
<td>5.0</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>Low or High</td>
<td>Cyanocobalamín</td>
<td>0.04</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Low or High</td>
<td>Vitamin A Palmitate</td>
<td>5.9</td>
</tr>
<tr>
<td>Zinc³</td>
<td>Low</td>
<td>Zinc Oxide</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Zinc Oxide</td>
<td>100</td>
</tr>
</tbody>
</table>

World Health Organization

Recommendations on Wheat and Maize Flour Fortification Meeting Report: Interim Consensus Statement
Essential Micronutrients

• **Vitamins**
  – Fat-soluble
    • Vitamin A, D, E, K
  – Water-soluble
    • Vitamin B1, B2, B3, B5, B6, B7, B9 (folic acid), B12, C, Choline

• **Macrominerals**
  – Calcium, Chloride, Magnesium, Phosphorus, Potassium, Sodium

• **Trace Minerals**
  – Copper, Iodine, Iron, Manganese, Molybdenum, Selenium, Zinc

• **Essential Fatty Acids**
  – Linolenic Acid (Omega-3), Linoleic Acid (Omega-6)
Vitamin D – where do we stand from a public health perspective?

- E.V. McCollum found cod liver oil with vitamin A degraded still cured rickets, and proposed vitamin D (McCollum, Biochem J, 1922, 53:293-8)
- In 1925, S. J. Cowell found that irradiated milk was much more effective than untreated milk in stimulating bone calcification in children (Cowell, BMJ, 1935, 587–642)
- In 1929, the Wisconsin Alumni Research Foundation (WARF, as in the anticoagulant drug “warfarin”) was founded to administer the patent for the milk irradiator.
- Vitamin D isolated and purified in 1932
- “Demand for vitamin D was driven primarily by the awareness-raising efforts of the public sector and the medical professionals who were themselves spurred by food industry advertising”. (Bishai, 2002)
- Several large dairies sought the American Medical Association’s seal of approval for their products.
Vitamin D – where do we stand from a public health perspective?

• Original focus on rickets and bone health
• Study has greatly expanded due to identification in 1971 of the active form (1α,25 (OH)₂ vitamin D), and in 1987 of the vitamin D receptor (VDR) and subsequent discovery of VDRs in almost every cell of the body
• More than 10,000 papers over past decade
• Consistent epidemiological evidence of correlation between low vitamin D status and higher rates of cardiovascular disease, infection, cancer, autoimmune disorders
• Clinical trials – few and inconsistent; major trials underway, results expected 2017
Vitamin D – metabolism

IOM and Endocrine Society recommendations

- IOM recommendations concluded evidence only strong enough for public policy recommendation for vitamin D in bone health (2010)
- Endocrine Society concurred but recommended somewhat higher levels in clinical practice (2011)
- Potential reverse J-curve for toxicity, not well established
- Risk assessment versus nutrient benefit
## Vitamin D guidelines, IOM (2010)

<table>
<thead>
<tr>
<th>Life stage group&lt;sup&gt;a&lt;/sup&gt;</th>
<th>EAR IU/d</th>
<th>Serum 250HD for the EAR&lt;sup&gt;e&lt;/sup&gt; ng/mL</th>
<th>RDA IU/d</th>
<th>Serum 250HD for the RDA&lt;sup&gt;f&lt;/sup&gt; ng/mL</th>
<th>UL IU/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 y (M+F)</td>
<td>400</td>
<td>16</td>
<td>600</td>
<td>20</td>
<td>2,500</td>
</tr>
<tr>
<td>4-8 y (M+F)</td>
<td>400</td>
<td>16</td>
<td>600</td>
<td>20</td>
<td>3,000</td>
</tr>
<tr>
<td>9-13 y (M+F)</td>
<td>400</td>
<td>16</td>
<td>600</td>
<td>20</td>
<td>4,000</td>
</tr>
<tr>
<td>14-18 y (M+F)</td>
<td>400</td>
<td>16</td>
<td>600</td>
<td>20</td>
<td>4,000</td>
</tr>
<tr>
<td>19-30 y (M+F)</td>
<td>400</td>
<td>16</td>
<td>600</td>
<td>20</td>
<td>4,000</td>
</tr>
<tr>
<td>31-50 y (M+F)</td>
<td>400</td>
<td>16</td>
<td>600</td>
<td>20</td>
<td>4,000</td>
</tr>
<tr>
<td>51-70 y (M)</td>
<td>400</td>
<td>16</td>
<td>600</td>
<td>20</td>
<td>4,000</td>
</tr>
<tr>
<td>51-70 y (F)</td>
<td>400</td>
<td>16</td>
<td>600</td>
<td>20</td>
<td>4,000</td>
</tr>
<tr>
<td>71+ y (M+F)</td>
<td>400</td>
<td>16</td>
<td>800</td>
<td>20</td>
<td>4,000</td>
</tr>
<tr>
<td>Pregnant or Lactating (F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-18 y</td>
<td>400</td>
<td>16</td>
<td>600</td>
<td>20</td>
<td>4,000</td>
</tr>
<tr>
<td>19-50 y</td>
<td>400</td>
<td>16</td>
<td>600</td>
<td>20</td>
<td>4,000</td>
</tr>
<tr>
<td>Infants (M+F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-6 mo</td>
<td>400&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td>1,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12 mo</td>
<td>400&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td>1,500</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Endocrine Society (US) recommendations for individuals at risk of vitamin deficiency

- Infants: 400 – 1000 IU per day
- Children up to 18 yr: 600-1000 IU/day
- Adults 19-70 yr: 1500-2000 IU/day

Holick, 2011, J Clin Endocrinol Metab, July 2011, 96(7):1911–1930
Differing definitions of adequacy

Diagnostic Cut-Offs of levels of serum 25[OH]D

<table>
<thead>
<tr>
<th>25[OH] Level (ng/mL)</th>
<th>25[OH]D Level (nmoL/L)</th>
<th>Laboratory Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>&lt;50</td>
<td>Deficiency</td>
</tr>
<tr>
<td>20–32</td>
<td>50–80</td>
<td>Insufficiency</td>
</tr>
<tr>
<td>54–90</td>
<td>135–225</td>
<td>Normal in sunny countries</td>
</tr>
<tr>
<td>&gt;100</td>
<td>&gt;250</td>
<td>Excess</td>
</tr>
<tr>
<td>&gt;150</td>
<td>&gt;325</td>
<td>Intoxication</td>
</tr>
</tbody>
</table>

Alshahrani, Nutrients 2013, 5, 3605-3616
Bone Health

- Vitamin D deficiency causes defects of bone mineralization
- Can lead to rickets in children and osteomalacia in adults
- Vitamin D increases absorption of calcium and phosphorus in bone (double for calcium, 30% increase for phosphorus)
- As vitamin D deficiency progresses, parathyroid glands are stimulated, increasing PTH levels, which in turn exacerbates vitamin D deficiency
- Fracture risk increased
- IOM conclusion – serum levels of 20 ng/ml (50 nmol/L) should be achieved for bone health
SE Asia

- Sunny region with sufficient sunlight for vitamin D production in the skin
- Few studies until recently
- Two countries now have published nationally-representative data: Thailand and Vietnam
- Singapore Health Promotion Board has unpublished data
- Studies show consistently higher than expected levels of vitamin D deficiency and insufficiency
- Attributable to lifestyle changes – less outdoor work, travel in cars or buses, more indoor recreational activities
Thailand Study

- Thailand: data from Thai 4th National Health Examination Survey conducted between August 2009 and March 2009
- Countrywide, 21 provinces
- N= 2,641 randomly selected from sample size of 21,960
- Ages 15-98 years
- LC-MS/MS

Thailand Study

- 5.7% having 25(OH)D concentrations <50 nmol/L, but significant geographic variation (Bangkok 14.3%)
- 45.2% with 25(OH)D level <75 nmol/L (including 75.5% of women in Bangkok)

Thailand Study

Table 4 Prevalence of vitamin D insufficiency by geographical region and gender

<table>
<thead>
<tr>
<th>Regions</th>
<th>Age, yrs (range)</th>
<th>Serum 25(OH)D levels</th>
<th>&lt; 75 nmol/L</th>
<th>&lt; 50 nmol/L</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Total</td>
<td>Men</td>
<td>Women</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Bangkok</td>
<td>15 - 93</td>
<td>66.7%</td>
<td>75.5%</td>
<td>64.6%</td>
<td>10.8%</td>
<td>24.2%</td>
<td>14.3%</td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>15 - 91</td>
<td>36.2%</td>
<td>59.2%</td>
<td>43.1%</td>
<td>2.1%</td>
<td>11.4%</td>
<td>6.5%</td>
<td></td>
</tr>
<tr>
<td>North</td>
<td>15 - 98</td>
<td>27.9%</td>
<td>50.8%</td>
<td>39.1%</td>
<td>0.9%</td>
<td>6.5%</td>
<td>4.3%</td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>15 - 91</td>
<td>25.1%</td>
<td>51.0%</td>
<td>34.2%</td>
<td>0.1%</td>
<td>3.7%</td>
<td>2.8%</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>15 - 92</td>
<td>29.4%</td>
<td>65.8%</td>
<td>43.8%</td>
<td>1.5%</td>
<td>12.9%</td>
<td>6.3%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>15 - 98</td>
<td>32.6%</td>
<td>57.3%</td>
<td>45.2%</td>
<td>1.9%</td>
<td>9.3%</td>
<td>5.7%</td>
<td></td>
</tr>
</tbody>
</table>

Vietnam study

- Vietnam, pregnant and non-pregnant women (n=541), urban and rural
- Mean level 81 nmol/L
- 7% having 25(OH)D concentrations <50 nmol/L
- 48% with 25(OH)D level <75 nmol/L

Hien, 2012, Matr. and Child Nutr., 8:533-539
Vietnam study

- Vietnam, pregnant and non-pregnant women, children (n=592 women, 525 children), urban and rural, nationally representative, geographically balanced
- Women - 17% having 25(OH)D concentrations <30 nmol/L; 40% 30-49.9 nmol/L
- Children - 21% having 25(OH)D level <30 nmol/L; 37% 30-49.9 nmol/L
- +90% of women and children 25 (OH) D level <75 nmol/L
- HPLC

Malaysian studies

- School age children: n=402
- 70.4% having 25(OH)D concentrations <50 nmol/L.
- 35.3% vitamin D deficient <37.5 nmol/L
- 37.1% vitamin D insufficient (>37.5 nmol/L, <50 nmol/L

Khor et al. BMC Public Health 2011, 11:95
Malaysian Studies

• Malaysia – university employees (mean age 48):
• 67.9% having 25(OH)D concentrations <50 nmol/L. (n=380)

Moy and Bulgiba, BMC Public Health 2011, 11:735
Indonesia and Malaysia

- Non-pregnant women 18-40 (urban): (n=502)
- 61% having 25(OH)D concentrations <50 nmol/L
- <1% with 25(OH)D level <17.5 nmol/L

Potential fortification – edible oil
Indonesia and Vietnam

<table>
<thead>
<tr>
<th>Target group</th>
<th>Average oil consumption (g/day)</th>
<th>Vitamin D supplied through vegetable oil fortification (µg/day)</th>
<th>% of IOM EAR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Level 7.5 µg/100 g</td>
<td>Level 10 µg/100 g</td>
</tr>
<tr>
<td>National fortification</td>
<td></td>
<td>Level 7.5 µg/100 g</td>
<td>Level 10 µg/100 g</td>
</tr>
<tr>
<td>Indonesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>20.5</td>
<td>1.23</td>
<td>1.64</td>
</tr>
<tr>
<td>Children &lt; 5 yr</td>
<td>17.3</td>
<td>1.04</td>
<td>1.38</td>
</tr>
<tr>
<td>Rich adults</td>
<td>26.0</td>
<td>1.56</td>
<td>2.08</td>
</tr>
<tr>
<td>Poor adults</td>
<td>23.0</td>
<td>1.38</td>
<td>1.84</td>
</tr>
<tr>
<td>Vietnam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women of reproductive age</td>
<td>11.1</td>
<td>0.67</td>
<td>0.89</td>
</tr>
<tr>
<td>Children 6-59.9 mo</td>
<td>6.0</td>
<td>0.36</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Based on fortification at WFP standard for vitamin D

Yang, 2013, Food Nutr Bull, vol. 34, suppl No. 2, S81-S89
WFP standard and new Tufts/USAID fortification recommendations for vitamin D

- World Food Program has standard for fortified palm oil, 2400-3600 IU per kilo of oil (60-90µg per kilo)
- Tufts review for USAID recent recommendation for all for food programs for edible oil to be fortified with 0.425 ppm vitamin D (17,000 IU or 425µg per kilo), which would provide 300 IU from a consumption of 20 grams of oil. Standard now adopted for all USAID edible oil
- Fortified oil permitted in many countries, including China, India, Morocco, Egypt, Uganda, expected for vitamin A in Indonesia in 2014

1) Webb, Delivering improved nutrition: recommendations for changes to US food aid products and programs. Tufts University Boston, MA: Tufts University, 2011
Food fortification
- Indonesia and Viet Nam

- **Indonesia** - fortifying wheat flour for a decade
  - Recently adopted mandatory fortification of edible oil with vitamin A effective from 2014, voluntary already permitted
  - Average edible oil consumption about 20 grams/day, reaching 70-80% of the country
  - Fortification at 425µg per kilo would provide roughly 300 IU per day (50% of RDA, 75% of EAR))

- **Vietnam** – voluntary wheat flour fortification, mandatory under discussion
  - Average consumption about 10 grams/day, reaching 70-80% of the country
  - Fortification at 425µg per kilo would provide roughly 150 IU per day (25% of RDA, 37.5% of EAR)
Vitamin D: non–skeletal functions

- Vitamin D receptors only identified in 1987 (cells identified in 1969 but not function), active form of vitamin D identified in 1971
- Vitamin D receptors are found in cells of bone, pancreatic β cells, parathyroid gland, brain, skin, prostate, testes, heart, skeletal muscle tissue, breast, liver, lung, intestine, kidneys, adipose cells and immune response cells, such as macrophages, dendritic cells and activated B- and T-cells
- Consistent, geographically diverse epidemiological evidence of link between lower levels of vitamin D status and higher levels of cardiovascular disease, diabetes, cancer, infection and immunity
- Mechanisms not clear, clinical trials show inconsistent results
Vitamin D – Cardiovascular Disease (CVD)

• Despite progress, 1-year mortality rates from congestive heart failure (CHF) remain high, 10-35%

• Several observational and prospective studies have shown a higher prevalence of vitamin D deficiency in CHF patients, and vitamin D deficiency is associated with more severe disease and higher rates of adverse outcomes

• Clinical trials inconsistent – different (sometimes small) doses, different states of deficiency, different end points

• Recent larger studies (Gotsman 2012, Vacek 2012, Thomas 2012, Schierbeck 2012) have shown benefits in CHF patients

• Mechanisms unclear
Supplementation trial – Vitamin D and Cardiovascular Disease

- Observational retrospective study, USA
- N=10,899
- Baseline: 70.3% < 30 ng/ml (75 nmol/L)
  - 29.7% > 30 ng/ml
- 5 years, 8 months

Vitamin D deficiency and risk of death from cardiovascular events

Table 2
Univariate analysis: odds ratio of death and major cardiovascular events if vitamin D deficient

<table>
<thead>
<tr>
<th>Event</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.95</td>
<td>2.135–4.073</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.16</td>
<td>1.012–1.334</td>
<td>0.03</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.83</td>
<td>0.693–0.984</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.31</td>
<td>2.018–2.633</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1.29</td>
<td>1.019–1.633</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.40</td>
<td>1.285–1.536</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio.

Table 3
Logistic regression analysis for death as dependent variable

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>2.71</td>
<td>2.062–3.573</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>2.64</td>
<td>1.901–3.662</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.45</td>
<td>1.114–1.891</td>
<td>0.006</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>3.29</td>
<td>2.359–4.596</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.53</td>
<td>1.183–1.969</td>
<td>0.001</td>
</tr>
</tbody>
</table>

(Vacek, 2012)
Vitamin D deficiency and risk of death from cardiovascular events

(Vacek, 2012)
Cohort Study

Vitamin D and Cardiovascular Disease

- Prospective cohort study
- N=1,801
- Baseline: 22.2% < 10 ng/ml (25 nmol/L); 70.3% < 30 ng/ml (75 nmol/L)
- Subject population with metabolic syndrome
- 7 years, 8 months
- Subjects above 30 ng/ml, reduced all-cause mortality (HR 0.75) and reduced CVD mortality (HR 0.67), dose dependent

Thomas, 2012, Diabetes Care, 35:1158-1164
Cohort Study

Vitamin D and Cardiovascular Disease

Thomas, 2012, Diabetes Care, 35:1158-1164
Cohort Study

Vitamin D and Cardiovascular Disease

- Prospective cohort study, London, UK
- N=5,409 men, median age 77 at baseline
- Median season-adjusted baseline 25(OH)D concentration 56 nmol/L
- Higher concentrations of 25(OH)D were inversely and approximately linearly (log –log scale) associated with vascular and non-vascular mortality throughout the range 40–90 nmol/L
- 13 year follow up
- Doubling in 25(OH)D concentration was associated with 20% lower vascular and 23% lower non-vascular mortality

Tomson, European Heart Journal (2013) 34, 1365–1374
Cohort Study
Vitamin D and Cardiovascular Disease

Tomson, European Heart Journal (2013) 34, 1365–1374
Vitamin D – Cardiovascular Disease (CVD)

Pourjabbar, Curr Opin Cardiol, 2013, 28:216-222
See also Al Mheid, European Heart Journal, 2013

ADH: antidiuretic hormone
CHF: congestive heart failure
ECF: extra-cellular volume
IL: interleukin
Na: sodium
RAAS: renin-angiotensin-aldosterone system
TNF: tumor necrosis factor
Vitamin D – Immunity

• Vitamin D receptor (VDR) found in the immune system agents: lymphocytes, monocytes and dendritic cells
• More than 30 positive effects of vitamin D on the immune system have been reported
• Beneficial effect of vitamin D on macrophages in phagocytizing the M. tuberculosis - RCT of a single oral dose of 2.5 mg ergocalciferol
• Roles in maturation of macrophages, including the production of macrophage-specific surface antigens, secretion of the lysosomal enzyme acid phosphatase and hydrogen peroxide
• RCTs show 50% reduction in dental carries
• Evidence of role in preventing autoimmune disorders and influenza

Rosen, Endocrine Reviews, June 2012, 33(3):456 –492
Vitamin D – Proposed Infection Mechanisms

Lang, Osteoporos Int, 2013, 24:1537-1553
Vitamin D – Proposed Infection Mechanisms

Monocytes and macrophages, dendritic cells, effector, and memory T and B lymphocytes all possess the enzymes to perform the hydroxylation steps to generate 1,25(OH)2D

Lang, Osteoporos Int, 2013, 24:1537-1553
### Vitamin D – Intervention trials, heterogeneous

<table>
<thead>
<tr>
<th>Infectious diseases</th>
<th>Reference</th>
<th>Study</th>
<th>Population</th>
<th>VitD supplementation</th>
<th>VitD status (post-replacement)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Design</td>
<td>Population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preventive therapy</td>
<td>Martineau et al. [142]</td>
<td>RCT</td>
<td>192 adults TB contacts (UK)</td>
<td>100,000</td>
<td>Once</td>
<td>S (91 %)</td>
</tr>
<tr>
<td>Adjunctive therapy</td>
<td>Morcos et al. [144]</td>
<td>RCT</td>
<td>24 children with pulmonary and extra-pulmonary TB (Egypt)</td>
<td>1,000/day</td>
<td>2 months</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Nursyam et al. [143]</td>
<td>RCT</td>
<td>67 adults with smear-positive pulmonary TB (Indonesia)</td>
<td>10,000/day</td>
<td>6 weeks</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Wejse et al. [141]</td>
<td>RCT</td>
<td>365 adults with pulmonary TB (Guinea-Bissau—Africa)</td>
<td>100,000</td>
<td>0, 2, and 5 months</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Martineau et al. [137]</td>
<td>RCT</td>
<td>146 adults with pulmonary TB (UK)</td>
<td>100,000</td>
<td>14, 28, and 42 days</td>
<td>S</td>
</tr>
<tr>
<td>Influenza</td>
<td>Aloia et al. [148]</td>
<td>RCT</td>
<td>208 postmenopausal women (USA)</td>
<td>800/day and 2,000/day</td>
<td>24 months and 12 months</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Urashima et al. [151]</td>
<td>RCT</td>
<td>167 children (Japan)</td>
<td>1,200/day</td>
<td>4 months</td>
<td>NR</td>
</tr>
</tbody>
</table>

A=no endpoints met;; B= some endpoints met; C=all endpoints met

From Lang, Osteoporos Int, 2013, 24:1537-1553
Vitamin D – Immunity

• Clear linkage between vitamin D and immune response at cellular level
• Mechanisms not yet well understood/elucidated
• Few large population studies, however some indication of benefits
Vitamin D – Cancer

• Solar ultraviolet-B (UVB)-vitamin D-cancer hypothesis was proposed by the Garland brothers at Johns Hopkins University in 1974. Found general inverse correlation between the regional doses of sunlight and colon cancer MRs. Paper published in 1980, and they later added breast and ovarian cancer to the list of cancers with reduced MRs in regions of higher solar radiation.

• Many ecological studies since have also found inverse relations between various cancers and vitamin D status
Vitamin D – Cancer

Cancers for which inverse correlations between incidence and/or mortality rates (MRs) were found with respect to indices of solar UVB dose

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>69.4</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Breast</td>
<td>26.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>24.5</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Prostate</td>
<td>22.0</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>20.1</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>10.2</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Leukemia</td>
<td>8.8</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Ovarian</td>
<td>8.4</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Gastric</td>
<td>7.3</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-Hodgkin’s lymphoma (NHL)</td>
<td>7.0</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Moukayed, Nutrients 2013, 5, 3993-4021
Vitamin D – Cancer

vitamin D intake of >400 IU/d from food and supplements was associated with a lower risk of lung cancer risk among never-smoking, postmenopausal women

<table>
<thead>
<tr>
<th>Total vitamin D intake (IU/d)²</th>
<th>Per 100 IU</th>
<th>&lt;100</th>
<th>100 to &lt;200</th>
<th>200 to &lt;400</th>
<th>400 to &lt;600</th>
<th>600 to &lt;800</th>
<th>≥800</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women (n)</td>
<td>1701</td>
<td>291</td>
<td>385</td>
<td>283</td>
<td>418</td>
<td>218</td>
<td>106</td>
<td>0.39</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00 (0.97, 1.02)</td>
<td>1.00 (Ref)</td>
<td>0.94 (0.80, 1.10)</td>
<td>0.90 (0.74, 1.09)</td>
<td>0.88 (0.73, 1.07)</td>
<td>0.90 (0.71, 1.14)</td>
<td>0.92 (0.69, 1.21)</td>
<td>0.39</td>
</tr>
<tr>
<td>Current smokers (n)</td>
<td>527</td>
<td>99</td>
<td>130</td>
<td>87</td>
<td>119</td>
<td>65</td>
<td>27</td>
<td>0.53</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.99 (0.94, 1.04)</td>
<td>1.00 (Ref)</td>
<td>1.15 (0.88, 1.52)</td>
<td>1.29 (0.91, 1.81)</td>
<td>1.04 (0.73, 1.49)</td>
<td>1.40 (0.91, 2.17)</td>
<td>1.03 (0.60, 1.76)</td>
<td>0.53</td>
</tr>
<tr>
<td>Former smokers (n)</td>
<td>896</td>
<td>147</td>
<td>201</td>
<td>135</td>
<td>236</td>
<td>112</td>
<td>62</td>
<td>0.76</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.01 (0.98, 1.04)</td>
<td>1.00 (Ref)</td>
<td>0.91 (0.73, 1.14)</td>
<td>0.77 (0.59, 1.01)</td>
<td>0.91 (0.70, 1.19)</td>
<td>0.81 (0.59, 1.11)</td>
<td>1.07 (0.74, 1.55)</td>
<td>0.76</td>
</tr>
<tr>
<td>Never smokers (n)</td>
<td>278</td>
<td>45</td>
<td>54</td>
<td>61</td>
<td>63</td>
<td>41</td>
<td>14</td>
<td>0.01</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.94 (0.88, 1.01)</td>
<td>1.00 (Ref)</td>
<td>0.68 (0.45, 1.03)</td>
<td>0.71 (0.45, 1.12)</td>
<td>0.55 (0.31, 0.83)</td>
<td>0.55 (0.31, 0.96)</td>
<td>0.37 (0.18, 0.77)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

cohort study: 128,779 postmenopausal women, 1993-2010

Vitamin D – Cancer

- Large prospective study (EPIC-Europe, 23 centers, 10 countries) reviewed 7,760 breast cancer cases out of 319,985 cohort. No relation found between estimated vitamin D intakes and cancer. However, no measurements of vitamin D status were taken (Abbas, Nutrition and Cancer, 65(2), 178–187).

- Hill’s criteria for causality have been applied to many types of cancer, finding them largely satisfied for breast and colorectal cancer.

- Well-designed RCTs are needed.
Vitamin D – Pregnancy and Infancy

• Vitamin D binding protein (DBP) increases 7-152% in pregnancy and 1,25(OH)₂D increases 47%
• Pooled analysis of trials using fixed-effects models suggested protective effects of supplementation on low birthweight (Thorne-Lyman, Paediatric and Perinatal Epidemiology, 2012, 26 (Suppl. 1), 75–90)
• Vitamin D stores of most children born to mothers with normal vitamin D status are depleted approximately 8 wks after delivery
• Emerging evidence suggesting plausible effects on intra-uterine growth restriction, pre-eclampsia, and both maternal and infant infections
Vitamin D – Pregnancy and Infancy

- Biggest percentage increase in length in first year of life, 50% increase
Vitamin D – safety

- one minimal erythemal dose (MED), provides the equivalent of 10,000–25,000 IU of oral vitamin D
- Excessive exposure to sunlight will not cause vitamin D intoxication because sunlight degrades any excess vitamin D
- Highest recorded individual serum 25[OH]D concentration obtained from sunshine was from a farmer in Puerto Rico with a level of 225 nmol/L [49].
- highest recorded individual 25[OH]D achieved from artificial ultraviolet light treatment sessions was 275 nmol/L [50].
Vitamin D – sunshine

• Active discussion among dermatologists on contribution to skin cancer
• Rates low in SE Asia
• Excessive exposure to sunlight will not cause vitamin D intoxication because sunlight degrades any excess vitamin D
• At 0-20 deg N/S latitude, exposure required (3 times a week, 50% of skin surface) ranges from 5 minutes (Fitzpatrick scale type 1, noon) to as much as 60 minutes (Fitzpatrick scale type 6, morning or late afternoon)
## Lawful additions of vitamin D - USA

<table>
<thead>
<tr>
<th>Category of food</th>
<th>21 CFR citation</th>
<th>Fortification status</th>
<th>Maximal level allowed</th>
<th>Estimate of fortified products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cereal flours and related products</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enriched Farina</td>
<td>137.305</td>
<td>Optional</td>
<td>350 IU/100 g</td>
<td>Few</td>
</tr>
<tr>
<td>Ready-to-eat breakfast cereals</td>
<td>137.305</td>
<td>Optional</td>
<td>350 IU/100 g</td>
<td>Most</td>
</tr>
<tr>
<td>Enriched rice</td>
<td>137.350</td>
<td>Optional</td>
<td>90 IU/100 g</td>
<td>None</td>
</tr>
<tr>
<td>Enriched corn meal products</td>
<td>137.260</td>
<td>Optional</td>
<td>90 IU/100 g</td>
<td>None</td>
</tr>
<tr>
<td>Enriched noodle products</td>
<td>139.155</td>
<td>Optional</td>
<td>90 IU/100 g</td>
<td>None</td>
</tr>
<tr>
<td>Enriched macaroni products</td>
<td>139.115</td>
<td>Optional</td>
<td>90 IU/100 g</td>
<td>Very few</td>
</tr>
<tr>
<td>Milk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid milk</td>
<td>131.110</td>
<td>Optional</td>
<td>42 IU/100 g</td>
<td>All</td>
</tr>
<tr>
<td>Acidified milk</td>
<td>131.111</td>
<td>Optional</td>
<td>42 IU/100 g</td>
<td>All</td>
</tr>
<tr>
<td>Cultured milk</td>
<td>131.112</td>
<td>Optional</td>
<td>42 IU/100 g</td>
<td>All</td>
</tr>
<tr>
<td>Concentrated milk</td>
<td>131.115</td>
<td>Optional</td>
<td>42 IU/100 g</td>
<td>All</td>
</tr>
<tr>
<td>Nonfat dry milk fortified with A and D</td>
<td>131.127</td>
<td>Required</td>
<td>42 IU/100 g</td>
<td>All</td>
</tr>
<tr>
<td>Evaporated milk, fortified</td>
<td>131.130</td>
<td>Required</td>
<td>42 IU/100 g</td>
<td>All</td>
</tr>
<tr>
<td>Dry whole milk</td>
<td>131.147</td>
<td>Optional</td>
<td>42 IU/100 g</td>
<td>All</td>
</tr>
<tr>
<td>Milk products</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yogurt</td>
<td>131.200</td>
<td>Optional</td>
<td>89 IU/100 g</td>
<td>Few</td>
</tr>
<tr>
<td>Low fat yogurt</td>
<td>131.203</td>
<td>Optional</td>
<td>89 IU/100 g</td>
<td>Few</td>
</tr>
<tr>
<td>Nonfat yogurt</td>
<td>131.206</td>
<td>Optional</td>
<td>89 IU/100 g</td>
<td>Few</td>
</tr>
<tr>
<td>Margarine</td>
<td>166.110</td>
<td>Optional</td>
<td>331 IU/100 g</td>
<td>Few</td>
</tr>
<tr>
<td>Calcium-fortified fruit juices and drinks</td>
<td>172.380</td>
<td>Optional</td>
<td>100 IU/RACC</td>
<td>NA</td>
</tr>
</tbody>
</table>

Calvo, 2004, Am J Clin Nutr
Vitamin D – conclusions

• Strong evidence of vitamin D levels in some countries in SE Asia of vitamin D levels less than recommended for bone health
• Clinical studies in remaining countries should be validated by nationally-representative data
• Dietary sources of products naturally containing vitamin D unlikely to be major contributors to improved vitamin D status in SE Asia
• Fortification of widely consumed products such as edible oil with vitamin D should be considered
• Research on non-skeletal functions of vitamin D should be intensified
Vitamin K – (Koagulation)

- Discovered in the early 1930s by the Danish biochemist Henrik Dam (Dam, Biochem J, 1934;28:1355–1359)
- Caused problems in chicks similar to scurvy
- Related to problems in neonatal mortality
- Prophylactic treatment with vitamin K reduced neonatal mortality rate among new born infants from 4.6% to 1.8%
- Dam and Doisy received the 1943 Nobel Prize

Dietary forms of vitamin K: phylloquinone (A) and menaquinones (B)
Vitamin K and health

• Vitamin K deficiency has been linked to
  – loss of bone mineral density (BMD)
  – increased fracture risk
  – arterial calcification or cardiovascular disease
  – Cancer
  – insulin resistance
  – Osteoarthritis
  – Chronic kidney disease
  – vascular calcification
  – inflammation

Vitamin K – Phylloquinone

- Green leafy vegetables contain the highest known phylloquinone concentrations and contribute ~60% of total phylloquinone intakes
- All recommended intake levels based on phylloquinone
- Indicator is level needed for proper blood coagulation

Table 1. Food Sources of Vitamin K

<table>
<thead>
<tr>
<th>Food</th>
<th>Vitamin K (µg per Serving)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Foods high in vitamin K</strong></td>
<td></td>
</tr>
<tr>
<td>Kale, frozen (1/2 cup cooked)</td>
<td>573</td>
</tr>
<tr>
<td>Collards, frozen (1/2 cup cooked)</td>
<td>530</td>
</tr>
<tr>
<td>Spinach, frozen (1/2 cup cooked)</td>
<td>514</td>
</tr>
<tr>
<td>Turnip greens, cooked (1/2 cup)</td>
<td>265</td>
</tr>
<tr>
<td><strong>Foods moderately high in vitamin K</strong></td>
<td></td>
</tr>
<tr>
<td>Brussels sprouts, cooked (1/2 cup)</td>
<td>110</td>
</tr>
<tr>
<td>Broccoli, cooked (1/2 cup)</td>
<td>110</td>
</tr>
<tr>
<td>Cabbage, cooked (1/2 cup)</td>
<td>82</td>
</tr>
<tr>
<td>Bibb lettuce, raw (1 cup)</td>
<td>56</td>
</tr>
<tr>
<td><strong>Foods low in vitamin K</strong></td>
<td></td>
</tr>
<tr>
<td>Potato, baked (1 medium, flesh and skin)</td>
<td>4</td>
</tr>
<tr>
<td>Raisins, golden seedless (1/2 cup)</td>
<td>3</td>
</tr>
<tr>
<td>Corn muffin (1 small, commercially prepared)</td>
<td>0</td>
</tr>
<tr>
<td>Orange, fresh (1 navel orange without skin)</td>
<td>0</td>
</tr>
</tbody>
</table>

Troung, J Evi Comp & Alt Med, 2001, 16 (1) 73-79
Vitamin K – Phylloquinone

• Adequate intake (AI) for vitamin K was set at 120 and 90 µg/day for men and women, respectively (IOM, 2001).

• In infants, the AI is set at 2–2.5 µg/day based on the estimated phylloquinone intake from breast milk. Infants exclusively breast-fed have an estimated daily intake of 0.5–2.6 µg (IOM, 2001), and they are at greater risk for vitamin K deficiency because breast milk is a poor dietary source of vitamin K.

• Infant formulas contain appreciable amounts of phylloquinone so the average daily intake of US infants 2–6 months of age is 63 µg (IOM, 2001)

• Infants are often born deficient in vitamin K because of poor maternal–fetal transfer across the placenta. In some countries, prophylaxis in the form of a single, intramuscular dose of 0.5–1 mg of phylloquinone is routinely administered as an effective intervention against hemorrhic bleeding at birth

• Half-life of 7.5 hours
Vitamin K – Menaquinones

• Major menaquinones contain 4–10 repeating isoprenoid units, indicated by MK-4 to MK-10; forms up to 13 isoprenoid groups have been identified
• Mostly derived from gut bacterial conversion of phylloquinone (only *Bacteroides* gut bacteria)
• Menaquinone-4 (MK-4) not mainly from bacterial production; instead it is alkylated from menadione present in animal feeds or is the product of tissue-specific conversion directly from dietary phylloquinone
• Poultry products are the primary dietary sources of MK-4 in the US food supply (Asia?)
• Menaquinone-7 (MK-7) is primarily found in natto, a soybean product that is fermented using *Bacillus natto*.
• Some menaquinones in cheese, also present in lower measure in eggs, meat, and fish (Asian diet??)
Vitamin K – Menaquinones

• MK-4 has half-life of about an hour, MK-7 has a half-life of 56-72 hours, while phylloquinone half life is 7.5 hours
• Mainly stored in liver

<table>
<thead>
<tr>
<th>Food item</th>
<th>United States</th>
<th>The Netherlands</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µg/100 g</td>
<td>µg/100 g</td>
<td>µg/100 g</td>
</tr>
<tr>
<td>Chicken, various cuts</td>
<td>13.6–31.6</td>
<td>5.8–11.3</td>
<td>27 ± 15</td>
</tr>
<tr>
<td>Pork or ham, various cuts</td>
<td>0.2–9.9</td>
<td>1.7–2.4</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>Beef, various cuts</td>
<td>1.1–9.3</td>
<td>0.7–1.3</td>
<td>15 ± 7</td>
</tr>
<tr>
<td>Milk, whole</td>
<td>0.8–1.0</td>
<td>0.7–0.9</td>
<td>2 ± 0.3</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>15.5</td>
<td>29.1–33.5</td>
<td>64 ± 31</td>
</tr>
</tbody>
</table>

Vitamin K – Menaquinones

- Discovery of amino acid γ -carboxy glutamic acid (Gla) in 1974 (now 17)
- Bone Glaprotein – osteocalcin, predominant noncollagenous protein in bone
- MatrixGla-protein (MGP) first described in 1983
- Strongest known inhibitor of tissue calcification
- Anticlotting drugs (e.g., warfarin) inhibit bone formation
- Long-term use of oral anticoagulants is considered a risk factor for developing osteoporosis.
- MGP - expressed in cartilage and the vasculature
- In healthy tissue expression is relatively low
- In the arteries MGP expression can be is up-regulated several orders of magnitude
Vitamin K – Menaquinones

• EFSA accepted health claim on vitamin K2 (and K1) in maintenance of bone
• Low dose supplementation with MK-7 (180 µg/day) over three years reduce loss of bone mass and decreased uncarboxylated osteocalcin (Knapen, Osteoporosis International, 2013, vol. 24, 9:2499-2507)
• High does supplementation with MK-4 (45 mg) in Thai postmenopausal women showed decrease of undercarboxylated osteocalcin, and 65% decreased bone resorption (Bunyarataveg, J Med Assoc Thai, 2001, 84 (suppl 2) S553-5597
Calcium link – bone loss and increased arterial calcification

- Vitamin K2 - demonstrated to be involved in the inhibition of vascular foci of calcification, especially through the carboxylation of MGP proteins that regulate calcium deposition in plaques

Flore, European Review for Medical and Pharmacological Sciences 2013; 17: 2433-2440
Vitamin A, D and K – Research Topics

• Potential interactions between fat-soluble vitamins A, D and K
• Potential vitamin A protection against vitamin D toxicity by exerting a vitamin K-sparing effect through the downregulation of MGP (Masterjohn, Medical Hypotheses (2007) 68, 1026–1034)
• One study, inverse association between ucOC and serum25(OH)D concentrations, and a subsequent reduction in ucOC by vitamin D supplementation.
• Cannot be explained by our current understanding of the biochemical role of vitamin K, but suggest that vitamin D may influence the ucOC level.
• In contrast, serum 25(OH)D and phylloquinone concentrations are not correlated (Szulc, J. Clin. Invest. 91, 1769–1774.)
Research issues – Vitamin A, D, and K

• Sources of phylloquinone and menaquinone in Asia diets
• Asian intakes of phylloquinone and menaquinone
• Stable isotope studies are required to quantify differences in absorption,
• bioavailability and distribution over the body between individual menaquinone forms and phylloquinone (Beulens, Br J Nutr, 2013, in press)
Research issues – Vitamin A, D, and K

- Magnesium plays an essential role in the synthesis and metabolism of vitamin D.
- High intake of total, dietary or supplemental magnesium was independently associated with significantly reduced risks of vitamin D deficiency.
- Recent review showed associations of serum 25(OH)D with mortality, particularly due to cardiovascular disease (CVD) and colorectal cancer, were modified by magnesium intake.
- Inverse associations were primarily present among those with magnesium intake above the median (Deng et al. BMC Medicine 2013, 11:187).
- Asian dietary intakes of magnesium??
Conclusions

• Public health actions are recommendable for vitamin D in SE Asia for bone health
• Considerable research needs to be undertaken on non-skeletal functions of vitamin D but there is considerable epidemiological evidence and biological plausibility for a beneficial role
• Vitamin K (and especially vitamin K2-menaquinone) are worthy of increased research in Asia but not yet demonstrated to be actionable for public health
• Interesting questions remain on interactions among the fat-soluble vitamins