Does it Matter where Patients Obtain their Nutrients?

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Disclosures

Boards –
NOF
ILSI
Showalter
Pharmavite

Grants –
NIH
Dairy Research Institute
Nestle
Tate and Lyle
NHANES continues to show Americans have a shortfall in *micronutrients*

**FIGURE 1: PERCENT BELOW ESTIMATED AVERAGE REQUIREMENT**

NHANES data used to estimate the percent of women ages 51

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**Intervention Strategies—how to decide**

- ‘Pop a Pill’
- *Eat your green leafy vegetables*
- *Just put it in the flour*

*Courtesy of Richard Deckelbaum*
Impact of added nutrients from enrichment and fortification in the US population on inadequate intake of certain vitamins using NHANES 2003-2006

Fulgoni, III et al., J Nutr 2011


Fulgoni, III et al., J Nutr 2011
NIH State-of-the-Science Conference Statement
Multivitamin/Mineral Supplements
and Chronic Disease Prevention
15–17 May 2006

“Finally, the present evidence is insufficient to recommend either for or against the use of MVMs by the American public to prevent chronic disease.”

“Half of American adults are taking MVMs and the bottom line is that we don't know for sure that they're benefiting from them. In fact, we're concerned that some people may be getting too much of certain nutrients,” J. Michael McGinnis, M.D., M.P.P., Senior Scholar with the Institute of Medicine of the National Academy of Sciences, who chaired the panel.”
Multivitamin use, folate, and colon cancer in women in the Nurses’ Health Study


Multivitamins showed 75% reduction in colon cancer starting at the 15th year.


http://www.myplate.gov
Comparison of Consumption to Recommendations

2010 Dietary Guidelines

Shortfall food groups for children and adults

Vegetables  Vit A, C, K, Mg
Fruits
Whole grains
Fluid milk and milk products - Ca, K, Vit D, Mg, P
Oils - Vit E
2010 Dietary Guidelines for Americans
Nutrients of Public Health Concern

• **Calcium** - The RDA ranges from 1000-1300 mg/d for > age 4y.

• **Potassium** - The Adequate Intake (AI) for potassium for adults is 4,700 mg per day.

• **Vitamin D** - The RDA ranges from 200 to 800 IU/d for those > age 9y.

**Bone Building Nutrient – Calcium**

• Calcium Requirements are Based on Bone Health

### NEW – Estimated Average Requirement

- 4-8 year olds – 800 mg/day
- 9-18 year olds – 1100 mg/day
- Adults <51 – 800 mg/day
- Males 51-70 – 800 mg/day
- Females 51-70 – 1,000 mg/day
- All adults >70 – 1,000 mg/day

**Sources**

- Foods
- Fortified foods
- Supplements

Institute of Medicine, National Academies, 2010
**Dietary Guidelines 2010** recommend 3 cups milk products per day (871/mg Ca)
- Go low-fat or fat-free
- If you don’t or can’t consume milk, choose lactose-free products or other calcium sources

**Median Milk Equivalent Intakes in US**
- 1.6 – adult men
- 1.2 – adult women
- 2.3 – adolescent boys, aged 14 - 18 y
- 1.5 – adolescent girls, aged 14 to 18 y
- 2.4 – boys, aged 9 to 13 y
- 1.9 – girls, aged 9 to 13 year

*Chee et al. Osteoporosis Int 14:828, 2003*

2 year RCT of milk supplementation (1200 mg Ca/ d)
BMD of spine and hip in 173 postmenopausal Chinese women

*Chee et al. Osteoporosis Int 14:828, 2003*
Milk Provides Essential Nutrients

3 cups low-fat milk provide about:

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>&gt;100%</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>99%</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>86%</td>
</tr>
<tr>
<td>Protein</td>
<td>54%</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>32%</td>
</tr>
<tr>
<td>Potassium</td>
<td>28%</td>
</tr>
<tr>
<td>Magnesium</td>
<td>25%</td>
</tr>
</tbody>
</table>

Vit B, Vit A, Zinc, and more…

Percentages for vit D and calcium based on EAR, percentages for all others based on RDA

NUTRIENT SOURCES

- the best and most economical source of the limiting nutrients is dairy
- diets low in dairy tend to be poor in other nutrients as well
- supplements usually cannot fill the total gap
Nutrient Rich Foods

*Nutrient density scoring (NRF 9.3)*

\[
NRF_{9.3} = \sum_{i=9}^{\text{nutrients}} \left( \%DV/100\text{kcal} \right) - \sum_{i=3}^{\text{nutrients}} \left( \%DV/100\text{kcal} \right)
\]

9 nutrients to encourage

- Protein
- Fiber
- Vitamin A
- Iron
- Calcium
- Vitamin C
- Potassium
- Magnesium
- Vitamin E

3 nutrients to limit

- Saturated Fat
- Added Sugars
- Sodium

Some Dairy NRF 9.3 Scores

<table>
<thead>
<tr>
<th>Food</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk, skim</td>
<td>123</td>
</tr>
<tr>
<td>Milk, chocolate, skim</td>
<td>56</td>
</tr>
<tr>
<td>Milk, 2% fat</td>
<td>43</td>
</tr>
<tr>
<td>Milk, full fat</td>
<td>38</td>
</tr>
<tr>
<td>Cheese, American or Cheddar</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Food</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yogurt, plain nonfat</td>
<td>94</td>
</tr>
<tr>
<td>Yogurt, plain low fat</td>
<td>84</td>
</tr>
<tr>
<td>Yogurt, nonfat milk, sweetened with low-calorie sweetener</td>
<td>122</td>
</tr>
<tr>
<td>Yogurt, vanilla nonfat</td>
<td>38</td>
</tr>
<tr>
<td>Yogurt, fruited, nonfat</td>
<td>3</td>
</tr>
</tbody>
</table>

Courtesy of Victor Fulgoni
Dairy products position well in nutrient, energy, and cost profiles

Nutrient quality based on healthy eating index for 9 nutrients to encourage and 3 to limit

Drewnowski and Fulgoni, AJCN In press

Fluid milk consumption is decreasing in Americans in all age groups
Growth expected to continue and accelerate

Total US Projected Yogurt Growth ($M)

12% CAGR Projection attainable due to changing trends

$5.8 $6.2 $6.6 $7.2 $7.4 $7.9 $8.8 $9.9 $11.1 $12.4 $13.9


Yogurt Consumption Associated with Better Diet Quality

Framingham Heart Study Offspring n=6526 Consumers (64% women, 41% men)

Wang et al., Nutr Res 33:16, 2013
Does the source of calcium matter?

Calcium Absorption (%)

Weaver and Heaney Calcif Tissue Int. 49:244, 1991
## Food sources of bioavailable calcium

<table>
<thead>
<tr>
<th>Food</th>
<th>Calcium Content Serving (mg)</th>
<th>Fractional Absorption (%)</th>
<th>Estimated Absorbable Ca/serving (mg)</th>
<th># Servings needed to = 1 c. milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk, yogurt</td>
<td>300</td>
<td>32.1</td>
<td>96.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Beans, dried</td>
<td>50</td>
<td>15.6</td>
<td>7.8</td>
<td>12.3</td>
</tr>
<tr>
<td>Broccoli</td>
<td>35</td>
<td>61.3</td>
<td>21.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Cabbage</td>
<td>79</td>
<td>52.7</td>
<td>41.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Kale</td>
<td>47</td>
<td>58.8</td>
<td>27.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Spinach</td>
<td>122</td>
<td>5.1</td>
<td>6.2</td>
<td>15.5</td>
</tr>
<tr>
<td>Tofu, calcium set</td>
<td>258</td>
<td>31.0</td>
<td>80.0</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Nearly 4 out of 10 Americans Don’t Consume Enough Calcium

NCI Usual Intake Method, NHANES 2009-2010, Day 1-2; Food sources only, Percent below estimated average requirement for calcium
Calcium supplementation is common

Percent calcium in common salts

<table>
<thead>
<tr>
<th>Salt</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate</td>
<td>40</td>
</tr>
<tr>
<td>Tricalcium phosphate</td>
<td>38</td>
</tr>
<tr>
<td>Dicalcium phosphate, dihydrate</td>
<td>36</td>
</tr>
<tr>
<td>Bone meal</td>
<td>31</td>
</tr>
<tr>
<td>Oyster shell</td>
<td>28</td>
</tr>
<tr>
<td>Dolomite</td>
<td>22</td>
</tr>
<tr>
<td>Calcium citrate</td>
<td>21</td>
</tr>
<tr>
<td>Calcium citrate malate</td>
<td>13</td>
</tr>
<tr>
<td>Calcium lactate</td>
<td>13</td>
</tr>
<tr>
<td>Gluconate</td>
<td>9</td>
</tr>
<tr>
<td>Glubionate</td>
<td>6.5</td>
</tr>
</tbody>
</table>

*Weaver, C.M. and Heaney, R.P. Ch. 9 Food Sources, Supplements and Bioavailability. In: Calcium in Human Health. Weaver, C.M. and Heaney, R.P., eds. Humana Press. 129-142, 2006.*
Calcium Absorption Efficiency from Various Salts at Loads of 200-300 mg in Premenopausal Women

<table>
<thead>
<tr>
<th>Salt</th>
<th>% Absorption Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca Carbonate</td>
<td>27</td>
</tr>
<tr>
<td>Calcium Citrate</td>
<td>10.4</td>
</tr>
<tr>
<td>Ca Citrate Malate</td>
<td>2.0</td>
</tr>
<tr>
<td>CaH PO₄</td>
<td>13.0</td>
</tr>
<tr>
<td>TCP</td>
<td></td>
</tr>
<tr>
<td>Calcium Oxalate</td>
<td>4.0</td>
</tr>
<tr>
<td>Calcium Lactate</td>
<td>41</td>
</tr>
<tr>
<td>Calcium Sulfate</td>
<td>57</td>
</tr>
</tbody>
</table>

Concern over Calcium Supplements
What Consumers Think…

- The number of consumers who take calcium calcium/vitamin D supplements has decreased from 22% in 2011 to 17% in 2012.

- Consumers trust their health care practitioners for advise on supplementation.

2012 CRN Consumer Survey on Dietary Supplements (n = 2006)

- Secondary analysis of studies designed to investigate bone
- Lacking baseline cardiovascular data
- Cardiovascular event ascertainment not standardized
  - Self-reported data
  - Potential for bias
- No dose-response relationship examined
- Intention to treat analysis, low compliance
- No underlying mechanism demonstrated

- Recommends against daily supplements <400 IU vitamin D3 and <1000 mg of Ca for the prevention of fractures in postmenopausal women.
- Current evidence is insufficient >400 IU vitamin D3 and >1000 mg Ca for the prevention of fractures in postmenopausal women, pre-menopausal women, and men.

NOF Responds to the U.S. Prevention Services Task Force Recommendation on Calcium and Vitamin D

“Calcium and vitamin D play a critical role, but are not enough alone to prevent fractures”....”We also know that osteoporosis medications don’t work without calcium and vitamin D”...

The controversy is unlikely to be resolved by epidemiological studies or secondary analysis of RCTs.

The best RCT is from the Women’s Health Initiative (WHI).
Women’s Health Initiative CaD Trial (n=68,719 postmenopausal women):
>5 Year CaD Intervention-related Health Outcomes in Subjects Adherent & Not Taking Baseline Supplements

Animal Models and Methodology

- Advantage: Directly assess causal relationships by feeding protocols sufficiently long to develop disease

- Disadvantage:
  - Animal models - different pathogenesis of coronary disease vs humans
  - Methodological barrier - advanced calcification necessary in order to detect via usual imaging & histology
Animal Models and Methodology

➢ We are using both new approach for measuring early Ca accumulation & new model that better represents human pathogenesis

Ossabaw Pig
Model for Soft Tissue Calcification?

Connie Weaver  
Nutrition Science

George Jackson  
AMS/Physics

J. Scott Radcliffe  
Animal Science

Sean Newcomer  
Health and Kinesiology

Meryl Wastney  
Kinetic Modeling

Bill Van Alstine  
Veterinary Medicine

Mike Sturek  
IU School Medicine
**41Ca kinetic modeling in Ossabaw Pig**

**Animal**: Ossabaw miniature pig
- when fed excess calorie atherogenic diet it develops Metabolic Syndrome (MetS) and progressed to coronary atherosclerosis

**Tracer**: 41Ca
- Long half-life ($T_{1/2} \approx 100,000$ yr)
- Can be monitored sensitively ($10^{-18}$ M) at the low levels expected in soft tissues

*Neeb ZP, et al., Comp Med 60:300-315, 2010*

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**MetS Pigs Had Higher $^{41}$Ca/Ca in Coronary Arteries than Lean Pigs**

![Bar Chart]

<table>
<thead>
<tr>
<th></th>
<th>$^{41}$Ca:Ca ratio ($\times 10^{-19}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean (n=7)</td>
<td>0.50</td>
</tr>
<tr>
<td>MetS (n=7)</td>
<td>1.50</td>
</tr>
</tbody>
</table>

*
Kinetics: Compartmental Model of Ca Metabolism

1: Blood + EVF
2: EVF + ICF
3: Exchangeable bone
4: Artery

- Mimic human metabolic syndrome and coronary artery disease on an atherogenic diet

Image borrowed from Sturek laboratory
• Research Goal:
  – To examine the impact of high dietary calcium from supplement (calcium carbonate) or dairy (non-fat dry milk) on cardiovascular function, vascular calcification and the progression of coronary artery disease.

**General Timeline**

- **Randomization:**
  - Control n=8
  - High Dairy n=8

- **1-2:** Blood Pressure, Weigh, Sling acclimation throughout
- **3:** Jugular Catheter Insertion and $^{44}$Ca dose
- **4:** Transport, Imaging, Sacrifice and Tissue Collection
- **5:** Blood & Urine collections
- **6:**......
• Plaque Wall Coverage (%) of coronary artery did not differ among dietary groups

• Stroke Volume and Ejection Fraction did not differ among groups
In vitro Wire Myography

- Proximal 1.5 cm of Left Anterior Descending (LAD)
- Examines functional responses and vascular reactivity of arteries
- Sensitive and early indicator of compromised cell function

Bradykinin (BK)

Endothelial Cell

Nitric Oxide (NO)

Sodium Nitroprusside (SNP)

Vascular smooth muscle

Cyclooxygenase

Prostacyclin (PGI2)

EDHF

K+

Relaxation!

GTP
cGMP

GC

L-Arginine

NO Synthase

AA
Bradykinin-Induced Relaxation of Coronary Artery

Sodium Nitroprusside-Induced Relaxation of Coronary Artery

Histology to assess plaque and calcification burden of coronary arteries

Von Kossa Stain
LAD Cross-section

Hematoxylin and Eosin Stain
LAD Cross-section
Coronary artery plaque coverage not different between treatments

![Means±SE chart]

- 3 cups of low-fat dairy product equivalents/day
  - 300mg calcium supplement for each serving missed

Dietary Guidelines
- 3 cups of low-fat dairy product equivalents/day
  - 300mg calcium supplement for each serving missed
3 Levels of Decision about Vitamin D Adequacy

1. Individual
2. Physician – Clinical Guidelines
3. Population - DRIs

IOM
Linked vitamin D status (25)HD) to requirements

- 40 nmol/L ≈ EAR
- 50 nmol/L ≈ RDA

Clinical Guidelines
- Deficiency < 50 nmol/L
- Target 75 nmol/L
Sources of Vitamin D

Fortified

Why expect vitamin D input to come from diet?

Populations at high risk for inadequate cutaneous production

- the elderly
- individuals with dark skin
- individuals living at temperate latitudes and higher
- invalids & shut-ins
- others who are not exposed to UVB radiation
Nearly 9 out of 10 Americans Don't Get Enough Vitamin D

Committee analysis of NHANES data: Confirmed published U-Shaped Relationship

Concern at higher Vitamin D status

NHANES African Americans, IOM Analysis, unpublished data

Melamed, Arch Int Med 2008
Bioavailability of Vitamin D – rich yeast compared to Vitamin D₃

Femur Midshaft

Both sources improve bone equally.
Dose effect P=0.03

Hohman et al. J Ag Fd Chem, 2011

Vitamin D and Ca Supplements Reduced All Cause Mortality by 7% compared to placebo in >70,000 median age 70y

Rejnmark et al., JCEM v97, 2012
Adequate Intake (AI) for potassium intakes set by the IOM. For children younger than 14 years old, the AI is less than 4700 mg per day.


Average K Intake Compared to Recommended Intakes

Dietary sources of potassium
Rich dietary sources of potassium (per portion) include:

- Baked sweet potato (694 mg)
- Baked white potato (flesh) (610 mg)
  - Yogurt (579 mg)
  - Prune juice (530 mg)
  - Carrot juice (517 mg)
  - Tuna (484 mg)
- Winter squash (448 mg)
  - Banana (422 mg)
  - Spinach (419 mg)
  - Tomato juice (417 mg)

Potatoes provide 19-20% of potassium in American diet

National Nutrient Database for Standard Reference, Release 25, 2012,
Effect of K citrate supplementation after 6 months in older men and women on net acid excretion and calcium retention.

K Citrate vs Placebo on BMD in 201 older adults

P<0.001
Conclusion

The source matters but intake matters more!