Vitamins and Supplements in Women’s Health

An Evidence-Based Approach

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I HAVE NO CONFLICTS OF INTEREST

Nutrition in a Bottle?
### Vitamins / supplements to be covered

- **Antioxidants**
  - Beta-carotene / Vitamin A
  - Vitamin E
  - Vitamin C
- **Folic acid / B-vitamins and homocysteine lowering**
- **Vitamin D / Calcium**
- **Omega – 3 polyunsaturated fatty acids**

### What percentage of Americans regularly use vitamin supplements?

- 0 to 20%
- 21 to 40%
- 41 to 60%
- 61 to 80%
- 81 to 100%

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### Vitamin Use in the U.S.A.

- 52% of Americans and increasing
  - More than doubled since 1970s
- $9.4 billion in 2009
- Reports from observational studies of diet are very popular with patients and are always in the news

### Why are they so popular?

- **Diseases of deficiency**
  - Vitamin C: Scurvy
  - Vitamin D: Rickets
  - Thiamine (B1): Beriberi
- **More is better philosophy in America**
  - Super-size me!
- **Self-efficacy / prevention / wellness**
Guiding Principle: Primum non nocere

When recommending a therapy to an otherwise healthy person (i.e. for disease prevention / wellness), you should have the highest level of evidence guiding your recommendation: randomized trials with patient-centered outcomes.

Why antioxidants?

• Laboratory and animal research show that antioxidants prevent the free radical damage that is associated with cancer, heart disease, and aging
• Antioxidants are provided by a healthy diet that includes a variety of fruits and vegetables
• Vitamins A, C, E, beta-carotene

β Carotene and Retinol Efficacy Trial (CARET)

• Subjects
  – 18,314 smokers, former smokers, asbestos
  – Age 45 - 74, mean 58. 34% women
  – Enrolled 1985, Seattle
• Follow-up 4 years
• RCT β-carotene 30 mg, Vit A 25000 IU
• Outcome: Lung CA, Death, CVD death

CARET Randomized Trial Results

> 18,000 participants followed for 4+ years on beta-carotene or placebo

Cumulative Mortality (%)
Vitamin E

- Factor X: a group of fat soluble compounds, the tocopherols
- Deficiency: Rare
- They are the primary fat soluble antioxidants
- US RDA 22 IU in men and women

Nurses’ Health Study (NHS)

- Subjects
  - 87,245 US Female Nurses
  - No CHD, Stroke or Cancer
- Follow-up 8 years
- Outcome: Non fatal MI, CHD Death

NHS Results for MI or CHD Death

<table>
<thead>
<tr>
<th>Quintiles of Vitamin E Intake</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
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</thead>
<tbody>
<tr>
<td>IU/d</td>
<td>2.8</td>
<td>4.2</td>
<td>5.9</td>
<td>17</td>
<td>208</td>
</tr>
<tr>
<td>RR</td>
<td>1.0</td>
<td>1.0</td>
<td>1.1</td>
<td>.74</td>
<td>.66</td>
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</table>

More is better: p-value for trend = 0.001

Women’s Health Study

- 40,000 healthy women at least 45 years old
- 10+ years of follow-up
- Vitamin E 600 IU every other day
  - No effect on cancer (RR 1.01)
  - No significant benefit for major CVD events
The answer!

- Meta-analysis of 47 high quality randomized trials of antioxidants
- 181,000 individuals
- 25,000 deaths

Death from any cause

- Vitamin A 16% increase
- Beta-carotene 7% increase
- Vitamin E 4% increase
- Vitamin C Trend towards increase (6%)

All p << 0.05 except vitamin C
Bottom line: actively discourage anti-oxidant use

Why?

- Postulated benefits of controlled oxidative damage (free radicals)
  - Kill bacteria
  - Eliminate damaged cells

Vitamin C…Brrrrr

- Marathon runners, skiers, soldiers on sub-arctic exercises
  - 50% reduction in the incidence of colds
- General public
  - No reduction in incidence
  - 10% reduction in duration
Vitamins, Homocysteine, and Heart Disease

Homocystinuria

• In-born error of metabolism (1962)
• Homocysteine levels in the blood: 100-400 µmol/L
• Normal homocysteine 8 to 12 µmol/L
• 1 in 150,000 live births

Homocystinuria: Clinical Features

• Premature cardiovascular disease
  – 50% experience major event by age 30 years
• Connective tissue defects
  – Osteoporosis
  – Lens dislocation
• Cognitive deficits

Homocysteine and Risk of Death

<table>
<thead>
<tr>
<th>Homocysteine</th>
<th>RR</th>
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</thead>
<tbody>
<tr>
<td>&lt; 9</td>
<td>1.0</td>
</tr>
<tr>
<td>9-14.9</td>
<td>3.3</td>
</tr>
<tr>
<td>15-19.9</td>
<td>6.3</td>
</tr>
<tr>
<td>≥ 20</td>
<td>9.9</td>
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</table>

Nygard, NEJM, 1997
Vitamins To Lower Homocysteine

- > 40 Randomized Clinical Trials
- Folic acid lowers homocysteine 25%
- Vitamin B12 lowers it an additional 7%

The Answer!

- Pooled meta-analysis of 8 large, high quality randomized trials
- 37,485 individuals
- 5,125 deaths
- 9,326 major vascular events
- 3,010 cancers

Folate / Homocysteine RCTs

- Homocysteine: 25% decrease
- Death: No effect: 1.02 (.97-1.08)
- CVD events: No effect: 1.01 (.97-1.05)
- Cancer: No effect: 1.05 (.98-1.13)

Folate does not prevent cancer or heart disease

Folate And Neural Tube Defects (NTD)

- 70% reduction in 2nd occurrence
  - 4 mg of folate
- 63% reduction in 1st occurrence
  - 0.4 mg of folate
- Since flour fortification
  - 46% reduction in NTD

Meta-analysis, Blencowe, IJE, 2010.
In the news

**MULTIVITAMINS**

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**Multivitamins... kill?**

- Iowa Women's Study
  - 38,772 women ages 55-69 followed 19 years
  - MVI: RR death 1.06 (1.02-1.10)
  - 2.4% absolute increase in mortality
  - NNH = 42

- Observational!

Mursu, Archives IM, 2011

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**That is the question!**

**TO D OR NOT TO D...?**

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**Nutrient of the year!**

The sun is rising on Vitamin D

Sales increased 82% from 2008 to 2009
Vitamin D

- Vitamin: prevents rickets in children
- Hormone: 1,25 dihydroxy-vitamin D
  - Intestinal and renal absorption of calcium, phosphate
  - Lowers PTH, prevents secondary hyperPTH
  - Neuromuscular function
  - Regulation of up to 10% of the human genome

Institute of Medicine Report

Panel reviewed 1000 studies on 25 health outcomes to update previous 1997 recommendations

Vitamin D: Adult Dietary Reference Intake* (U.S.)

- Age
- 1-70 years 600 IU / day
- > 70 years 800 IU / day

*Institute of Medicine, 2010: Sufficient to meet the needs of virtually all people.

Vitamin D Status: Levels of 25(OH)D

<table>
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<tr>
<th>Status</th>
<th>ng/mL</th>
<th>nmol/L</th>
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<tr>
<td>Deficient</td>
<td>&lt; 12</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Insufficient</td>
<td>12 – 20</td>
<td>30 - 50</td>
</tr>
<tr>
<td>Sufficient</td>
<td>≥ 20</td>
<td>≥ 50</td>
</tr>
<tr>
<td>Potentially harmful</td>
<td>≥ 50</td>
<td>≥ 125</td>
</tr>
</tbody>
</table>

*hypercalcemia, hyperphosphatemia*

1 ng/mL = 2.5 nmol/L
Vitamin D levels in Americans

Prevalence of inadequate 25(OH) vitamin D among American women ≥14 years old by IOM definitions

- < 12 ng/ml 10 to 12% At risk of deficiency
- < 20 ng/ml 34 to 39% At risk of inadequacy
- < 30 ng/ml ~80%

Why so little D?

Vitamin D and Sunlight

- Most of the world relies on natural exposure to sunlight to maintain adequate levels
- Sunscreens of > 8 SPF can prevent synthesis
- Smog, smoke, window glass, even window screens can reduce synthesis

Sources of Vitamin D

- 400 IU/ tsp
- 100 IU/ 8 fl oz
- 20 IU/ egg yolk
- 400 IU/3oz
- 90 IU/ 8 fl oz
- 2700 IU/ serving

Treatment Of Low Vitamin D

- At risk for Deficiency (< 12 ng/ml)
  - 50,000 IU of Vitamin D2 or D3 per week for 6-8 weeks and then 800-1000 IU per day
- Nutritional Insufficiency (< 20 ng/ml)
  - 800-1000 IU per day
  - Goal will be reached in 3 months
- Monitor at 3 months
- Tolerable upper limit for Vitamin D is 4000 units per day per IOM.
Vitamin D supplements: Two forms

- Vitamin D₂: ergocalciferol
  - (milk fortification, U.S. supplements, plants)
- Vitamin D₃: cholecalciferol
  - (*natural*: sunlight, fatty fish)

Should we be recommending supplements for prevention?

Systematic Review for fracture prevention: Conflicting Results

- 25 RCTs of vitamin D with fracture outcomes
- Heterogeneity: Population
  - Average age 53 to 85 years
  - Nursing homes versus community
  - Prior hip fracture versus no prior fractures
- Heterogeneity: Treatment
  - 300 to 500,000 IU D₂ or D₃
  - Daily to annually
  - With or without calcium

Best Early Trial: Benefit!

- Chapuy NEJM 2002
  - 3270 women in 180 nursing homes in France
  - Daily 800 IU D₃ + 1200 mg calcium versus placebo
  - Hip fractures
    - 5% versus 7%, p = 0.004
  - Non-vertebral fracture
    - 10% versus 13%, p < 0.001

Most Recent Trial: Harm!

- Sanders JAMA 2010: The VITAL D trial
  - 2256 women ≥70 years in Australia with risk factors for hip fracture
  - Annual 500,000 IU D₃ without calcium. (~1400 IU/d)
  - Falls: 15% increase with vitamin D (p = 0.03)
  - Fractures: 26% increase (p = 0.047)
**Why The Variation?**

- **Significant contributors**
  - Calcium supplementation with vitamin D

- **Not significant**
  - Age, sex, baseline vitamin D level
  - Vitamin D type, dose, frequency
  - Calcium for control group

**Note:** All of the studies that included calcium used daily dosing of vitamin D

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**Vitamin D and Fractures**

- **Daily vitamin D plus calcium reduces fracture risk**
  - 18% for hip fractures
  - 14% for all fractures

- **Greater absolute benefit in high risk groups**
  - Age > 70 years
  - Prior fracture
  - Low baseline intake

- **Harms are uncommon, though recent concerns about calcium supplementation and heart disease**

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**Harms of Vitamin D ± Calcium**

- **Slight excess of hypercalcemia, constipation**
  - Approximately 1% more in vitamin D group

- **Significant increase in kidney stones over 7 years**
  - 2.5% versus 2.1% (HR 1.17, 95% CI 1.02 to 1.34) in WHI

- **Non-significant trend towards fewer deaths**
  - In WHI: 63 fewer deaths, 68 more kidney stones

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**Vitamin D: The New Panacea**

- **Reduces the following diseases...**
  - Cancer (Colon, Breast, Prostate, Pancreatic, ...)
  - Cardiovascular disease
  - Multiple sclerosis, Type 1 DM, RA
  - Influenza and URIs
  - Chronic pain
  - Total Mortality!
Serum 25-hydroxyvitamin D and all-cause mortality in 13,331 NHANES 3 participants

Meta-analysis of D and Total Mortality

- 24 randomized trials, n = 88,097
  - 87% female
  - Median age 70
- Vitamin D alone did not affect mortality
- Vitamin D + calcium reduced total mortality 9% (95% CI 2% to 16%)
- NNT = 151 over 3 years

Upper Respiratory Tract Infection By Serum 25-hydroxyvitamin D Level And Season

RCT: VIDARIS Trial, JAMA, October 2012

- 322 healthy adults in New Zealand
- 100,000 IU D3 monthly
- 18 months follow-up

<table>
<thead>
<tr>
<th>25(OH) D</th>
<th>URI incidence</th>
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<tbody>
<tr>
<td>Vitamin D 48 ng/mL</td>
<td>3.7 infections/person</td>
</tr>
<tr>
<td>Placebo 25 ng/mL</td>
<td>3.7 infections/person</td>
</tr>
</tbody>
</table>
What About Calcium?

Calcium Does a Lot!

- Ion transport across cell membranes
  - Nerve transmission
  - Muscle contraction (including the heart)
- Blood pressure regulation
- Blood clotting
- Secretion of hormones, digestive enzymes, neurotransmitters
- Activation of many cellular enzymes

IOM Report Calcium Recommendations

DRI – Adequate Intake
- Adolescents: 1300 mg/day
- Women and men (19-50 years): 1000 mg/day
- Women and men (>50 years): 1200 mg/day

Current intake levels:
- Women: ~1/3 of their recommended intake
- Men: ~3/4 of their recommended intake

Tolerable Upper Intake Level: 2500 mg/day
Yet Another Caveat

- 1000 mg calcium supplement may be too much: 24% increase MI (p=.004), 15% increase MI or Stroke (p=.009)

Vitamin D and Calcium Take Home Points

- Vitamin D insufficiency is common
- 25 OH vitamin D is a predictor of bone health in terms of fracture risk and risk of falls
- Target frail, older patients
- 800 IU of vitamin D3 per day is sufficient
  - Ensure adequate calcium intake
- Testing is expensive and unnecessary
- Evidence is weak for other diseases

Epidemiology

- Sinclair 1944: CHD rare in Greenland Eskimos despite a high fat diet with few vegetables, fruits, or complex carbohydrates
Omega-3 Fatty Acids: Observations

• Oily, cold water fish = best sources of Ω-3 fatty acids
  – EPA = eicosapentanoic acid
  – DHA = docosahexanoic acid
• People who consume fish rich in EPA and DHA have fewer fatal and non-fatal CV events
• 1-2 servings/week fish associated with 36% less risk of CV death and 17% less total mortality

How Much Should I Consume?

American Heart Association 2003 Guidelines

• Healthy people:
  – At least 2 servings of fish/week AND plant-based sources of Ω-3’s
• People with CAD:
  – 1 gram of EPA + DHA/day

Randomized trials of Ω-3s in heart disease

• GISSI-Prevention: Lancet 1999
  – 11,323 patients within 3 months of MI
  – 1 gram EPA + DHA
  – 21% reduction total mortality
  – 45% reduction in sudden death
• 2010: 5 studies. NEJM, Circ, JAMA, BMJ
  – Not even a trend towards benefit for post-MI, CVD or atrial fibrillation
• Intubated with acute lung injury: JAMA 2011
  – Harm: 3 extra days in ICU, trend - more death (p=0.054)

2012 Meta-analysis of RCTs

• 14 RCTs: 20,485 patients with CVD
• 0.4 to 4.8 g/day omega-3 fatty acids
• 1-5 years of follow-up, mean 2 years
• No significant reduction in
  – All-cause mortality
  – Sudden cardiac death
  – Major cardiovascular events

Kwak, Archives IM, 2012
Since meta-analysis

• ORIGIN trial: RCT in NEJM 6/11/12
  – 12,536 patients with DM or high sugar
  – 1 g daily of omega-3 x 6.2 years
  – NO reduction in death, CVD events

• Risk and Prevention Trial: NEJM May 2013
  – 12,513 patients at high risk for CVD
  – 1 g daily of omega-3 x 5 years
  – NO reduction in death, CVD events

Summary Omega-3 FA / Fish oil

• No benefit in modern era of medical therapy for vascular disease

• No significant harms: trend towards fewer deaths in most trials

We Evolved to Eat REAL Food

• When nutrients are isolated from whole foods, they don’t always act the same

Dietary studies: Randomized

• RCT Mediterranean diet vs. low fat
  – Spain, 7500 people, 5 years FU
  – Enriched for olive oil or nuts
  – 30% reduction in CVD events

• Recommend: fruits, vegetables, legumes, tomato sauce, fish, wine

• Discourage: sodas, sweets, pastries, red and processed meats.
Dietary studies: Observational

- Adventist Health Study 2
  - 73,000 participants; 2570 deaths
  - 5.8 years follow-up
- Compare: vegans, pesco-, lacto-ovo-; and semi-vegetarians to non-vegetarians
- Outcome: lowest mortality in pesco-vegetarians and vegans (15-20%).

Orlich, JAMA IM, 2013

Summary

- Beta-carotene Discourage - harmful
- Vitamin E Discourage - harmful
- Folate For child-bearing age to prevent neural tube defects
- Vit D + calcium Older, frail patients to prevent fractures & falls
- Omega-3s No benefit

Michael Pollan’s Recommendations

- Eat real food
- Not too much
- Mostly plants
- Some fish

Thank you!

QUESTIONS?
If I Decide to Take a Supplement, How Can I Find a Quality Product?

Use Information from Independent Testing Laboratories

- ConsumerLab.com

Learn As Much As You Can

- Office of Dietary Supplements
  http://ods.od.nih.gov
- Medline: CAM on PubMed
- Natural Standard database ($)  
  www.naturalstandard.com

Look for a “Seal of Approval”
The final word

“Vitamins taken in excess of the dose required to prevent deficiency states have not improved our patients’ health and may harm them. We should recommend therapies to prevent disease in healthy patients only when randomized trials unequivocally demonstrate that net benefits outweigh net harms, and we should continue to emphasize the importance of a nutritious diet, regular physical activity, and no smoking as the best ways to optimize health.”

Tice JA. Archives Intern Med 2010.

Observational studies: Healthy user effect

- Vitamin supplement users have healthier lifestyles:
  - More educated
  - More physically active
  - More likely to eat a healthy diet
  - Thinner
  - Less likely to smoke
  - Less likely to have diabetes
  - Have lower blood pressure