Vitamins and Supplements in Primary Care

An Evidence-Based Approach

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I HAVE NO CONFLICTS OF INTEREST

Nutrition in a Bottle?

Vitamins / supplements to be covered

• Beta-carotene / Vitamin A
• Vitamin E
• Vitamin C
• 
• 
•
What percentage of Americans regularly use vitamin supplements?

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

Vitamin Use in the U.S.A.

- More than doubled since 1970s
- $9.4$ billion in 2009
- Reports from observational studies of diet are very popular in the news

Guiding Principle: Primum non nocere

When recommending a therapy to an otherwise healthy person (i.e. for disease prevention), you should have the highest level of evidence guiding your recommendation.

Why antioxidants?

- 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
Anti-oxidants: Animal Data example

- Antioxidant-treated rabbits had 50% fewer aortic lesions than lovastatin treated rabbits

Beta-carotene: Sources / Effects

- Red, yellow, orange fruits and veggies
  - Carrots, tomatoes, sweet potatoes, yellow squash, spinach in US
- Uses
  - Vision, cellular differentiation, immune function, antioxidant
- Toxicity
  - Skin yellowing

CARET Trial Results

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

Vitamin E

- Factor X: a group of fat soluble compounds, the tocopherols
- Deficiency: Rare
- The are the primary fat soluble anti-oxidants
- US RDA 8 mg in women, 10 mg men
Nurses’ Health Study (NHS)

- 87,245 US Female Nurses
- No CHD, Stroke or Cancer

Follow-up 8 years

Outcome: Non-fatal MI, CHD Death

Stampfer, NEJM, 1993

NHS Results for MI or CHD Death

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

P Value for trend 0.001

Stampfer, NEJM, 1993

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)
  - Non-significant trend towards benefit for major CVD events

Lee, JAMA, 2005

The answer!

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

Bjelakovic, JAMA, 2007
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
Actively discourage anti-oxidant use


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>
</tr>
</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 $p&lt;0.001$</td>
</tr>
</tbody>
</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

Clarke, Archives IM, 2010.

### Folate / Homocysteine RCTs

- Homocysteine 25% decrease
- Death  No effect: 1.02 (0.97-1.08)
- CVD events  No effect: 1.01 (0.97-1.05)
- Cancer  No effect: 1.05 (0.98-1.13)

Folate does not prevent cancer or heart disease

Clarke, Archives IM, 2010.
Folate And Neural Tube Defects (NTD)

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

Meta-analysis, Blencowe, IJE, 2010.

TO D OR NOT TO D...?

That is the question!

VITAMIN D: My patient

Veronica D. is a 57 year old woman with Paget’s disease, diabetes, depression, chronic pain and recent unexplained iron deficiency who comes in for a health care maintenance exam. You order a vitamin D level because of concerns about malabsorption and because every other internist is ordering vitamin D. It comes back as 7 ng/mL. What did you do...? What do you do now?

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

Dietary Reference Intakes for Calcium and Vitamin D

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

Vitamin D Status: Levels of 25(OH)D

<table>
<thead>
<tr>
<th>Status</th>
<th>ng/mL</th>
<th>nmol/L</th>
</tr>
</thead>
<tbody>
<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: Adult Dietary Reference Intake* (U.S.)

<table>
<thead>
<tr>
<th>Age</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-70 years</td>
<td>600 IU / day</td>
</tr>
<tr>
<td>&gt; 70 years</td>
<td>800 IU / day</td>
</tr>
</tbody>
</table>

*Institute of Medicine, 2010: Sufficient to meet the needs of virtually all people.
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 18%  At risk of deficiency
< 20 ng/ml  34 to 39%  At risk of inadequacy
≤ 30 ng/ml  ~80%

Why so little D?

NHANES 2003-2006

Vitamin D and Sunlight

• sunlight to maintain adequate levels
• Sunscreens of > 8 SPF can prevent synthesis
• Smog, smoke, window glass, even window screens can reduce synthesis

We Can't Make Adequate D3 From Sunlight in Winter Above 35°N

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)
  - 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
    - 200 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/day)
  - 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

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

### Harms

- 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
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.

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

The VITamin D and Omega-3 Trial (VITAL): Design

20,000 Initially Healthy Men and Women
(Men ≥60 yrs; Women ≥65 yrs)

Vitamin D3
(2000 IU/d; N=10,000)

Placebo
N=10,000

EPA+DHA
(1 gm/d; N=5000)

Placebo
N=5000

EPA+DHA
(1 gm/d; N=5000)

Placebo
N=5000

Mean Treatment Period = 5.0 years
Blood collection in ~16,000, follow-up bloods in 2000
Primary Outcomes: Cancer (total) and CVD (MI, stroke, CVD death)

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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 (Note: no RDA)
- 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=.003).
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

OMEGA 3 FATTY ACIDS

Epidemiology

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

Classification of Dietary Fat

- Saturated
  - Beef
  - Dairy
- Mono-unsaturated
  - Olive oil
  - Canola oil
- Poly-unsaturated
  - Omega-3
    - Fish, walnuts, flaxseed, soybean
  - Omega-6
    - Safflower oil, corn oil, peanuts, soybean
- Trans
  - Hydrogenated oils (Processed foods)
Omega-3 Fatty Acids

- 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

Omega-3 Fatty Acid Intake

- 80% decrease in intake of Ω-3’s since 1900
- Ω-6 intake has increased
- Higher ratio of Ω-6/Ω-3 associated with greater inflammation
- Inflammation now felt related to development of cardiac disease, cancer, Alzheimer’s and other degenerative diseases

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

Systematic reviews of RCTs

Table 3. Cochrane Reviews of Omega-3 Fatty Acids

<table>
<thead>
<tr>
<th>Disease name</th>
<th>Cochrane review conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Insufficient evidence to recommend a role for omega-3 fatty acids*</td>
</tr>
<tr>
<td>Cancer cachexia</td>
<td>Insufficient data*</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>Insufficient benefit in persons with intermittent claudication, but no evidence of consistent improvement in clinical outcomes*</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Regular omega-3 supplements may provide some benefits for persons with cystic fibrosis*</td>
</tr>
<tr>
<td>Dementia</td>
<td>Insufficient quality of evidence to support use of omega-3 fatty acids in dementia*</td>
</tr>
<tr>
<td>Diabetes type 2</td>
<td>Insufficient evidence to support use of omega-3 fatty acids in diabetes type 2*</td>
</tr>
<tr>
<td>Kidney transplant recipients</td>
<td>Insufficient evidence to recommend fish oil therapy*</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Insufficient evidence to support use of omega-3 fatty acids in inflammatory bowel disease*</td>
</tr>
<tr>
<td>Cataracts</td>
<td>Insufficient evidence to support use of omega-3 fatty acids in cataracts*</td>
</tr>
<tr>
<td>Stroke</td>
<td>Insufficient evidence to support use of omega-3 fatty acids in stroke*</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Insufficient evidence to support use of omega-3 fatty acids in heart failure*</td>
</tr>
</tbody>
</table>

* Evidence is insufficient to support use of omega-3 fatty acids in these conditions.
Randomized trials 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: 6 studies. NEJM, Circ, JAMA, BMJ
  - Not even a trend towards benefit for post-MI, CVD or atrial fibrillation

Summary Omega-3 FA / Fish oil

- Evidence is conflicting – less convincing in modern era of medical therapy for vascular disease
- VITAL trial should help with multiple outcomes
- No significant harms: trend towards fewer deaths in most trials

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
- Omega-3s: Stay tuned

Michael Pollan’s Recommendations

- Eat real food
- Not too much
- Mostly plants
  - Some fish
If I Decide to Take a Supplement, How Can I Find a Quality Product?

Use Information from Independent Testing Laboratories

- ConsumerLab.com

Look for a “Seal of Approval”

Contents Certified
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

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 IM, 2010.