Calcium and Vitamin Supplements

What does the evidence tell us?

Jeffrey A. Tice, MD
Division of General Internal Medicine
University of California, San Francisco

I HAVE NO CONFLICTS OF INTEREST

Annals of Internal Medicine this week...
**Vitamins / supplements to be covered**

- Antioxidants
  - Beta-carotene / Vitamin A
  - Vitamin E
  - Vitamin C
- Folic acid / B-vitamins and homocysteine lowering
- Vitamin D / Calcium

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

“To improve or maintain overall health.”

- 52% of Americans and increasing
  - More than doubled since 1970s
- $37 billion on supplements in 2014
- Reports from observational studies of diet are very popular with patients and are always in the news
- MVI, Vitamins C & D, calcium, omega-3s

**Dickinson, JACN, 2014**

**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

**β Carotene and Retinol Efficacy Trial (CARET)**

- Subjects
  - 18,000 smokers
  - Ages 45 – 74
- 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

Vitamin E

- The primary fat soluble anti-oxidants
- US RDA 22 IU in men and women
- Deficiency: Rare

Nurses’ Health Study (NHS)

- Subjects
  - 87,000 US 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>
</tr>
</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>
</tr>
</tbody>
</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
  - No effect on major CVD events

Lee, JAMA, 2005.

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**The answer!**

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


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**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**


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**Vitamins, Homocysteine, and Heart Disease**


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 (.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

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

• 70% reduction in 2nd occurrences
  – 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.

TO D OR NOT TO D...?

That is the question!

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 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?

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

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

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

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
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!

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

<table>
<thead>
<tr>
<th>Season</th>
<th>&lt;10 ng/mL</th>
<th>10 to &lt;30 ng/mL</th>
<th>≥30 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**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>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>48 ng/mL</td>
</tr>
<tr>
<td>Placebo</td>
<td>25 ng/mL</td>
</tr>
</tbody>
</table>

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**Serum 25-hydroxyvitamin D and all-cause mortality in 13,331 NHANES 3 participants**

- Adjusted All-Cause Mortality Rate Ratio (95% CI)
- Serum 25(OH)D Level, ng/mL
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

Rejnmark, JCEM, August 2012

The Answer!

- VITAL (VIT D and OmegA-3 Trial) US
  - RCT 2000 IU Vitamin D3: n = 25,874
- D-Health Australia
  - RCT 60,000 IU/month: n = 20,000
- FIND (Finnish Vitamin D Trial)
  - RCT 1600/3200 IU Vitamin D3: n = 18,000
- VIDAL UK
  - RCT 100,000 IU/month: n=20,000
- Results expected in 2017

What About Calcium?

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
Available supplements

- Calcium Carbonate
  - Cheap: Tums, many others
  - Requires acid for absorption (take with food)
- Calcium Citrate
  - Absorbed without acid

Yet Another Caveat

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

Annals IM 10/25/2016

- Calcium intake in RDA range is not associated with CVD in health adults
- Editorial
  - Imperfect evidence
  - Diet is safer (fewer kidney stones)
  - Low fat dairy, tofu, canned fish with bones: 2-3 servings/day

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
**General principles**

- Eat enough to avoid deficiency
- Doses significantly above RDAs are unhelpful and may be harmful

**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

**Michael Pollan’s Recommendations**

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

Thank you!

**QUESTIONS?**
**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

**Observational studies: Healthy user effect**

- Vitamin supplement users have healthier lifestyles (confounding):
  - 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

**In the news**

**MULTIVITAMINS**

**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
    - Number needed to harm = 42

  - Observational!

Mursu, Archives IM, 2011
MVI for Male MDs?

- Gaziano, PHS II, JAMA, 10/17/12
  - 14,641 male physicians ≥ 50 years followed for 11 years
  - RR 0.92, 95% CI 0.86 – 1.0, p=0.04 for the incidence of all cancers
  - 4 interventions, 4+ outcomes, only this one statistically significant
  - Can you say multiple comparisons?

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

Epidemiology

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

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

Kwak, Archives IM, 2012
Summary Omega-3 FA / Fish oil

- No benefit 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

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.

Estruch, NEJM, 2013

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.

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 IM, 2010.