“Vitamins and Supplements: Knowing your ABCs (and D and E’s)”

Jeffrey A. Tice, MD

BIOGRAPHY:

Jeffrey A. Tice, MD is an Associate Professor of Medicine in the Division of General Internal Medicine at UCSF. After his undergraduate work at Dartmouth, Dr. Tice received his MD at UCSF and completed residency training in Internal Medicine and a Clinical Research Fellowship at UCSF. He has been the Principal Investigator on studies of vitamins and supplements for the prevention of heart disease, breast cancer and for the treatment of menopausal symptoms. He also performs systematic reviews of new medical technologies for the California Technology Assessment Forum. Dr. Tice’s work has been indexed at the National Library of Medicine and is widely cited in coverage decisions by organizations around the world.

BIBLIOGRAPHY:


Vitamins and Supplements

An Evidence-Based Approach

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Nutrition in a Bottle?

I HAVE NO CONFLICTS OF INTEREST
### 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%

### 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
Who uses vitamin supplements?

- 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

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

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: Safe!
**ß 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 ß-carotene 30 mg, Vit A 25000 IU**
- **Outcome**: Lung CA, Death, CVD death

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**CARET Randomized Trial Results**

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

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**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**

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**Vitamin E: Sources**

- Foods high in E: E in the US Diet
- Wheat germ: Tails and oils (20%)
- Vegetables off: Vegetables (15%)
- Egg yolks: Leaf (15%)
- Nuts: Desserts (10%)
- Green Vegetables: Breakfast cereal (5%)
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

Stampfer, NEJM, 1993

NHS Results for MI or CHD Death

Quintiles of Vitamin E Intake

<table>
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<tr>
<th></th>
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<th>3rd</th>
<th>4th</th>
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<td>IU/d</td>
<td>2.8</td>
<td>4.2</td>
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<td>208</td>
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<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

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)
  - No significant 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

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

Hemila, Chalker, Cochrane review, 2012.

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>
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<tr>
<th>Homocysteine</th>
<th>RR</th>
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<tr>
<td>&lt; 9</td>
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<tr>
<td>9-14.9</td>
<td>3.3</td>
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<tr>
<td>15-19.9</td>
<td>6.3</td>
</tr>
<tr>
<td>≥ 20</td>
<td>9.9 p&lt;0.001</td>
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</table>

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.

Folic acid in early pregnancy: a public health success story

Sarah G. O’Keeffe, Richard H. Fischl, Jees L. Miller, Gary M. Shaw, and Anthony R. Saffo

MULTIVITAMINS

In the news
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
  - B6, folate, iron, magnesium, zinc, and copper supplements also associated with increase in death
    - Observational!

Mursu, Archives IM, 2011

That is the question!

TO D OR NOT TO D...?

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

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

Vitamin D Status: Levels of 25(OH)D

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<tr>
<th></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>
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<tr>
<td>Insufficient</td>
<td>12 – 20</td>
<td>30 - 50</td>
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<tr>
<td>Sufficient</td>
<td>≥ 20</td>
<td>≥ 50</td>
</tr>
<tr>
<td>Potentially harmful</td>
<td>≥ 50</td>
<td>≥ 125</td>
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</table>

(hypercalcemia, hyperphosphatemia)

1 ng/mL = 2.5 nmol/L

*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?

**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

**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)**
  - 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 D$_2$:** ergocalciferol
  - (milk fortification, U.S. supplements, plants)
- **Vitamin D$_3$:** cholecalciferol
  - ("natural": sunlight, fatty fish)

Should we be recommending supplements for prevention?

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**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

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

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
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!

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
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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<tr>
<td>Vitamin D</td>
<td>48 ng/mL</td>
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<tr>
<td>Placebo</td>
<td>25 ng/mL</td>
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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
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 from randomized trials

- 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 level is a predictor of bone health: increased risk of falls and fractures
- 800 IU of vitamin D3 per day is sufficient
  - Ensure adequate calcium intake: supplement with the lowest possible amount
- Testing is expensive and unnecessary
- Evidence is weak for other diseases

OMEGA 3 FATTY ACIDS

A fishy story...
Epidemiology

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

Classification of Dietary Fat

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

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
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%).
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

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

Thank you!

QUESTIONS?
Use Information from Independent Testing Laboratories

- ConsumerLab.com

Look for a “Seal of Approval”

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.