The Vital Fat-Soluble Vitamins

Presented by Chris Masterjohn, PhD

September, 2013 Regional Wise Traditions Conference
Portland, OR

This content of this talk is the independent work of Chris Masterjohn and does not necessarily represent the positions or opinions of the University of Illinois.
The Major Sources of Vitamins A and D

Liver – Vitamin A

Sunshine – Vitamin D

Cod Liver Oil – Vitamins A and D
My Wise Traditions Articles Through Spring, 2007

- **Fall, 2004** – Vitamin A: The Forgotten Bodybuilding Nutrient
- **Spring, 2005** – The China Study
- **Fall, 2005** – Dioxins in Animal Foods: A Case for Vegetarianism?
- **Winter, 2005/Spring, 2006** – Vitamin A on Trial: Does Vitamin A Cause Osteoporosis?
- **Fall, 2006** – From Seafood to Sunshine: A New Understanding of Vitamin D Safety
- **Spring, 2007** – On the Trail of the Elusive X-Factor: A 62-Year Mystery Finally Solved
Vitamin A Intake Greater Than 5,000 IU Associated With the Risk of Hip Fracture in Sweden

Vitamins A and D Protect Against Each Other’s Toxicity and Increase the Need for Each Other

- Massive doses of vitamin A cause bone loss in animals, but massive doses of vitamin D offer complete protection.

- Massive doses of vitamin D cause soft tissue calcification in animals, but massive doses of vitamin A offer complete protection.

- Even modest amounts of one vitamin can deplete the storage supply of the other.

- These interactions occur even if vitamin D is provided by ultraviolet light or both vitamins are provided by injection.
Vitamin A Contributes to Bone Loss Only When Vitamin D Is Limiting

Elevated Phosphorus
Depressed Calcium
Bone Loss
The Major Sources of Vitamins A and D

Liver – Vitamin A

Sunshine – Vitamin D

Cod Liver Oil – Vitamins A and D
Good Vitamin, Bad Vitamin: Repeating A Historical Mistake?
Cod Liver Oil Prevented and Cured Deficiencies of Both Vitamins A and D

Corneal ulceration due to **xerophthalmia**, prevented by vitamin A.

**This is rare!**

Bowed and poorly mineralized legs due to **rickets**, prevented by vitamin D.

**This is important!**
Dogs Fed Vitamin A-Deficient Diets Developed Pneumonia

- Olive Oil: Soft bones, bronchial pneumonia.
- Butter (A): Soft bones, free of infection.
- Cod Liver Oil (A+D): Well mineralized bones, free of infection.

Vitamin A, Not Vitamin D, Protected Against Infection in Rats

"The importance of vitamin D has attracted great attention recently, and it has even been suggested that preparations of vitamin D can be safely substituted for cod-liver oil in medical treatment. The work above described shows that this teaching is erroneous, and that, although vitamin D controls, probably absolutely, the calcification of bones and teeth, it has no direct power to promote resistance to infection in the same way as vitamin A. If a substitute for cod-liver oil is given it ought to be at least as powerful as this oil in its content of both vitamins A and D."

Vitamin A Is the Anti-Infective Vitamin!

Cod Liver Oil Decreases the Incidence of Colds

One tbsp CLO (15,000 IU A; 2,000 IU D) per day, Dec-March, n=313.

Cod Liver Oil Decreases Time Missed From Work

One tbsp CLO (15,000 IU A; 2,000 IU D) per day, Dec-March, n=313.

Vitamins A and D Only Protect Against Colds When Combined

54 “chronic or frequent cold sufferers” aged 7-49 given 9,000-40,000 IU A, 120,000-300,000 IU D, or both, daily Sept-June for three years.

Vitamins A and D Proved Toxic Alone But Not in Combination

Percentage of Subjects Who Developed Symptoms of Toxicity

54 “chronic or frequent cold sufferers” aged 7-49 given 9,000-40,000 IU A, 120,000-300,000 IU D, or both, daily Sept-June for three years.

Two Models of Synergy

Vitamin A → Molecular Process → Clinical Outcome

Vitamin D → Molecular Process

Vitamin A → Molecular Process

Vitamin D → Clinical Outcome
Vitamin A Deficiency: Replacement of Normal Epithelial Tissue With Keratinized Tissue Sabotages Defense Against Pathogens

Normal Pseudo-stratified Columnar
- Ciliated
- Goblet cells produce mucous
- Defense against pathogens

Replacement w/ Keratinized In Deficiency
- Hyperkeratosis
- Loss of normal tissue function, including the first line of immune defense.
- Xerophthalmia

Vitamin A Supports the Immune System in Many Ways

Vitamin A also does the following:

- Supports Natural Killer Cell Activity
- Enhances T Cell Proliferation
- Supports Killer T Cell Function
- Supports Helper T Cell Activity
- Regulates Activation, Proliferation, and Survival of B Cells
- Increases Production of Zinc-Dependent Metalloproteinases

Vitamin D Stimulates Production of Antimicrobial Peptides

Cathelicidins and their derivatives are also effective against:

- *Candida albicans*
- *Streptococcus aureus*
- Group A *Streptococcus* (*S. pyogenes* or GAS)
- *E. faecalis*
- *Pseudomonas aeruginosa*
- *E. coli*
- lentiviruses and retroviruses (e.g. HIV)
Activation of Vitamins A and D

Vitamin A (Retinol) → Retinal → All-Trans Retinoic Acid (ATRA)

Vitamin D → Calcidiol (25(OH)D) → Calcitriol (1,25(OH)₂D)

Retinoic Acid (9CRA) → 9-Cis Retinoic Acid (9CRA)
Vitamins A and D Are Molecular Partners

**Vitamin A-Responsive Genes**

ATRA

- RAR
- RXR

**Regulation of**

**Vitamin D-Responsive Genes**

Calcitriol

- VDR
- RXR

RAR – Retinoic Acid Receptor; VDR – Vitamin D Receptor; RXR – Retinoid X Receptor
Two Models of Synergy

- Vitamin A
  - Molecular Process
  - Clinical Outcome
- Vitamin D
  - Molecular Process (crossed out)
  - Clinical Outcome
- Vitamin A
  - Molecular Process
  - Clinical Outcome
- Vitamin D
  - Molecular Process
A Revised Model of Synergy

Vitamin A → Molecular Process

Vitamin A → Molecular Process

Vitamin D → Molecular Process

Clinical Outcome
Vitamins A and D Synergistically Increase the Production of Osteocalcin

Is the Mechanism of Vitamin D Toxicity Similar to That of Vitamin A But Reversed?

A → Elevated Phosphorus
Depressed Calcium
→ Bone Loss

A → Hypercalcemia
→ Soft Tissue Calcification

D
A Third Synergistic Partner: Vitamin K₂!

Leafy Greens – Vitamin K₁

Animal Fats and Fermented Foods – Vitamin K₂
Vitamin K Activates Proteins By Giving Them the Ability to Bind Calcium

```
peptide

<table>
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<tr>
<th>COO^-</th>
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<tbody>
<tr>
<td>CH_2</td>
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<tr>
<td>CH_2</td>
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</table>

Glutamate residue in peptide

Vitamin K carboxylase

CO_2

\[ \text{Ca}^{2+} \]

\[ -\text{OOC} \]

\[ \text{CH} \]

\[ \text{CH}_2 \]

\[ \text{COO}^- \]

\[ \gamma\text{-carboxy glutamate peptide} \]
```
Vitamins A and D Synergistically Increase the Production of Osteocalcin

Osteocalcin Only Accumulates in Bone Matrix After Activation by Vitamin K

Accumulation of Osteocalcin In the Extracellular Matrix

- Control
- Vitamin D
- Vitamin K
- Vitamin D + K

Vitamin K<sub>2</sub> Protects Against Calcification of Blood Vessels and Heart Valves

Nutritional Epidemiology

Dietary Intake of Menaquinone Is Associated with a Reduced Risk of Coronary Heart Disease: The Rotterdam Study<sup>1</sup>

Johanna M. Geleijnse,*† Cees Vermeer,** Diederick E. Grobbee,‡ Leon J. Schurgers,** Marjo H. J. Knapen,** Irene M. van der Meer,* Albert Hofman,* and Jacqueline C. M. Witteman<sup>‡</sup>

*Department of Epidemiology & Biostatistics, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands; **Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands; ‡Department of Biochemistry, Cardiovascular Research Institute Maastricht, University of Maastricht, Maastricht, The Netherlands; and ‡Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

ABSTRACT Vitamin K-dependent proteins, including matrix Gla-protein, have been shown to inhibit vascular calcification. Activation of these proteins via carboxylation depends on the availability of vitamin K. We examined whether dietary intake of phyloquinone (vitamin K-1) and menaquinone (vitamin K-2) were related to aortic calcification and coronary heart disease (CHD) in the population-based Rotterdam Study. The analysis included 4807 subjects with dietary data and no history of myocardial infarction at baseline (1990–1993) who were followed until January 1, 2000. The risk of incident CHD, all-cause mortality, and aortic atherosclerosis was studied in tertiles of energy-adjusted vitamin K intake after adjustment for age, gender, BMI, smoking, diabetes, education, and dietary factors. The relative risk (RR) of CHD mortality was reduced in the mid and upper tertiles of dietary menaquinone compared to the lower tertile [RR = 0.73 (95% CI: 0.45, 1.17) and 0.43 (0.24, 0.77), respectively]. Intake of menaquinone was also inversely related to all-cause mortality [RR = 0.51 (0.75, 0.89) and 0.74 (0.59, 0.98)].
Vitamin K$_2$ Intake Is Associated With a Reduced Incidence of CHD

Coronary Heart Disease Incidence

Risk Ratio

Intake of Vitamin K$_2$ (μg)

<21.6 21.6-32.7 >32.7

0.0 0.2 0.4 0.6 0.8 1.0

41% *

Vitamin K₂ Intake Is Associated With a Reduced Incidence of CHD

Vitamin K2 Intake Is Associated With Reduced Aortic Calcification

Likelihood of Having Severe Aortic Calcification

Intake of Vitamin K2 (µg)

<21.6 21.6-32.7 >32.7
0.0 0.2 0.4 0.6 0.8 1.0
Odds Ratio

MGP Knockout Mouse Is Shorter In Stature Than Normal Mouse and Suffers From Soft Tissue Calcification and Spontaneous Fractures

Warfarin During Pregnancy Causes Underdevelopment of Middle Third of the Face

The Maxilla Constitutes the “Middle Third of the Face”
Synergy Between Vitamins A, D, and K₂

- Vitamins A and D cooperate to tell cells which proteins to make, and how much of them to make.

- Vitamin K₂ activates those proteins by giving them the ability to bind calcium.
Vitamin D toxicity redefined: Vitamin K and the molecular mechanism

Christopher Masterjohn *

Weston A. Price Foundation, 4200 Wisconsin Ave., NW, Washington DC 20016, United States

Received 13 September 2006; accepted 14 September 2006

Summary  The dose of vitamin D that some researchers recommend as optimally therapeutic exceeds that officially recognized as safe by a factor of two; it is therefore important to determine the precise mechanism by which excessive doses of vitamin D exert toxicity so that physicians and other health care practitioners may understand how to use optimally therapeutic doses of this vitamin without the risk of adverse effects. Although the toxicity of vitamin D has
My Hypothesis

Overproduction of Defective Vitamin K-Dependent Proteins

Soft Tissue Calcification
Tufts Confirms: Vitamin A Curbs The Excessive Production of Vitamin K-Dependent Proteins Otherwise Induced by Vitamin D

Vitamin A Normalizes the Production of **Defective** MGP That Otherwise Increases With Vitamin D

Vitamins A and D Synergize to Maximize the Amount of *Active* MGP Produced

Vitamins A and D Synergize to Minimize the *Proportion* of MGP That Is *Defective*
A New Model of Vitamin D Toxicity

Toxicity of Vitamins A and D Due to Imbalance

- Elevated Phosphorus
- Depressed Calcium
- Bone Loss

- Overproduction of Defective Vitamin K-Dependent Proteins
- Soft Tissue Calcification
Synergy Between Vitamins A, D, and K₂

Activated Vitamin K-Dependent Proteins

Strong Bones and Teeth
Protection Against Soft Tissue Calcification
Adequate Growth
Unanswered Questions

• Can the mechanistic understanding generated by the Tufts study be replicated in a study using dietary vitamins rather than the activated hormone forms?

• Does vitamin K protect against vitamin D toxicity like vitamin A does? Or is it the vitamin K-dependent enzyme rather than the amount of vitamin K that is limiting?

• Can this be replicated in other species?
Vitamin K₂ Intake Associated With a Reduced Risk of Advanced Prostate Cancer

Vitamin K$_2$ Reduces the Risk of Liver Cancer in Women by 87%

The Many Functions of Vitamin A

- Essential to good vision, especially night vision.
- Essential to male and female reproduction.
- Essential to proper development of organs and tissues.
- Aids in the production of steroid hormones.
- Protects against kidney stones.
- May protect against asthma.
- Supports dopamine signaling; may protect against depression and support focused, goal-oriented behavior.
- Protects against fatty liver disease.
- Protects against oxidative stress and exposure to environmental toxins.
Many Roles for Vitamin D?

- Rickets and osteomalacia
- Hypocalcemia
- Convulsions, tetany and heart failure in the newborn
- Osteoporosis
- Heart Disease
- High blood pressure
- Obesity

- Arthritis
- Mental Illness
- Chronic Pain
- Muscular weakening
- Radiation poisoning
- Diabetes
- Multiple sclerosis
- Other autoimmune diseases
Making the Most of the Fat-Soluble Vitamins: Zinc, Magnesium, Fat, Carbs, Carbon Dioxide, and Thyroid!

(Oh my!)
Vitamin A Helps Convert Impulses of Light Into Visual Images

http://lpi.oregonstate.edu/infocenter/vitamins/vitaminA/visualcycle.html
Zinc Is Sometimes Necessary to Correct Vitamin A-Related Visual Function
A “Zinc Finger Motif” Activates the Nuclear Receptors For the Fat-Soluble Vitamins
Zinc Is Needed For Vitamin A to Promote Proper Eye Development

Percent of Children With Abnormalities in Conjunctival Surface

- Placebo: 13%
- Zinc: 15%
- Vitamin A: 6%
- A + Zinc: 0%

Zinc is Found Most Abundantly in Oysters, Beef, and Cheese

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<th>Food</th>
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<tr>
<td>Oysters</td>
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<tr>
<td>Ground Beef</td>
<td>3.9-4.1</td>
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<tr>
<td>Liver</td>
<td>3.1-3.9</td>
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<td>Cheese</td>
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<tr>
<td>Eggs</td>
<td>1.1</td>
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<tr>
<td>Legumes</td>
<td>0.6-1.0</td>
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<td>Milk</td>
<td>0.4</td>
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<tr>
<td>Grains and Cereals</td>
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<td>Vegetables</td>
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<tr>
<td>Fruit</td>
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The Role of Magnesium

Vitamin D

\[ \text{PTH} \]

\[ \text{Mg}^{2+} \]

\[ 25(\text{OH})\text{D} \]

\[ \text{Mg}^{2+} \]

\[ 1,25(\text{OH})_2\text{D} \]

\[ \text{Mg}^{2+} \]

Calcium Absorption

\[ \text{Mg}^{2+} \]

Distribution of Calcium to Blood, Bones, Teeth, and Storage Vesicles

\[ \text{Mg}^{2+} \]

Parathyroid Gland
Magnesium is Rich in Many Foods, But Not Meat Or Refined Carbs

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<tr>
<th>Food</th>
<th>Magnesium (mg/100 g)</th>
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<td>Caviar</td>
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<td>Buckwheat</td>
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<td>Whole Wheat</td>
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<tr>
<td>Liver</td>
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<tr>
<td>Enriched White Flour</td>
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<tr>
<td>Table Sugar</td>
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[www.nutritiondata.com](https://www.nutritiondata.com)
Butterfat Increases the Absorption of Vitamin E

Canola Oil Increases Absorption of Carotenes From Salad

Saturated Fats Are Superior At Promoting Fat-Soluble Vitamin Absorption

Percent Absorption of Beta-Carotene From a Liquid 28% Fat Test Meal

- Safflower Oil: 10.9%
- Beef Tallow: 59%

Vitamin K Activates Proteins With Carbon Dioxide, Giving Them the Ability to Bind Calcium
Activation of Vitamin K-Dependent Proteins Depends on the Concentration of CO$_2$

**Blood Results for Gary Taubes**

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**03/30/2011 07:16AM**

**QUEST DIAGNOSTICS FAX REPORT**

**TAUBES, GARY**

**DOB:** 04/30/1956  **AGE:** 54  
**GENDER:** M  **FASTING:** U

**SPECIMEN INFORMATION**

**SPECIMEN:** BA3869843  
**REQUISITION:** SCRIPT,

**COLLECTED:** 03/22/11 16:16  
**RECEIVED:** 03/22/11 16:18  
**REPORTED:** 03/30/11 07:15

**COMMENTS:** The original copy of this report was printed on: 03/25/11 at 04:35

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<td>98-110 mmol/L</td>
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<td>L</td>
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<td>7-25 mg/dL</td>
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<tr>
<td>eGFR</td>
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[http://garytaubes.com/2011/04/before-sugar-were-talking-about-cholesterol/]
Carbon Dioxide – What’s the Limiting Atom?

\[ \text{CO}_2 \]

Carbon Dioxide

Glucose

Fat
The Respiratory Quotient (CO$_2$/O$_2$) Increases Proportionally With Carbohydrate Utilization
Production of CO$_2$ Declines on a Low-Carbohydrate Diet

Low-Carbohydrate Diets Lower Blood Levels of Carbon Dioxide

20 adult patients requiring artificial ventilation fed a standard or low-carb, high-fat diet through a feeding pump

Low-Carbohydrate Diets Lower the Breathing Rate

20 adult patients requiring artificial ventilation fed a standard or low-carb, high-fat diet through a feeding pump

Low-Carbohydrate Diets Reducing Breathing Rate and Time on Ventilator

20 adult patients requiring artificial ventilation fed a standard or low-carb, high-fat diet through a feeding pump

Intense Exercise Increases Carbon Dioxide

Working at a Standing Desk Increases Carbon Dioxide Production

[Graph showing increased caloric expenditure and carbon dioxide production for standing desks compared to sitting desks.]

20 healthy young adult men and women performed crossword puzzles and wordfinds for 45 minutes.

Thyroid Hormone Increases the Production of Vitamin K-Dependent Proteins in Rats

Thyroid Hormone Prevents Blood Vessel Calcification

Conclusions

- Vitamins A, D, and K₂ cooperate together to protect soft tissues from calcification, provide for adequate growth, and nourish strong bones and teeth.

- Vitamin A is found primarily in liver and cod liver oil, while carotene-rich plant foods can also support vitamin A status.

- Vitamin D is found primarily in cod liver oil and fatty fish, and obtained from sunshine.

- Vitamin K₂ is found primarily in animal fats and fermented foods, especially egg yolks and hard cheeses.

- Zinc and magnesium are needed to support the fat-soluble vitamins. The best way to obtain these minerals is to eat a diet inclusive of both animal foods and plant foods but devoid of refined carbohydrates.

- Fat is necessary to absorb fat-soluble vitamins, while carbohydrate, thyroid hormone, and exercise may help optimize carbon dioxide production for the activation of vitamin K-dependent proteins.
Thank You!

Chris Masterjohn, PhD
Blog: The Daily Lipid
http://blog.cholesterol-and-health.com