

What Is the Strength of the
Evidence for Supplement Use for
a Healthy Immune System?
(Echinacea, vitamin E, zinc,
omega-3 fatty acids)

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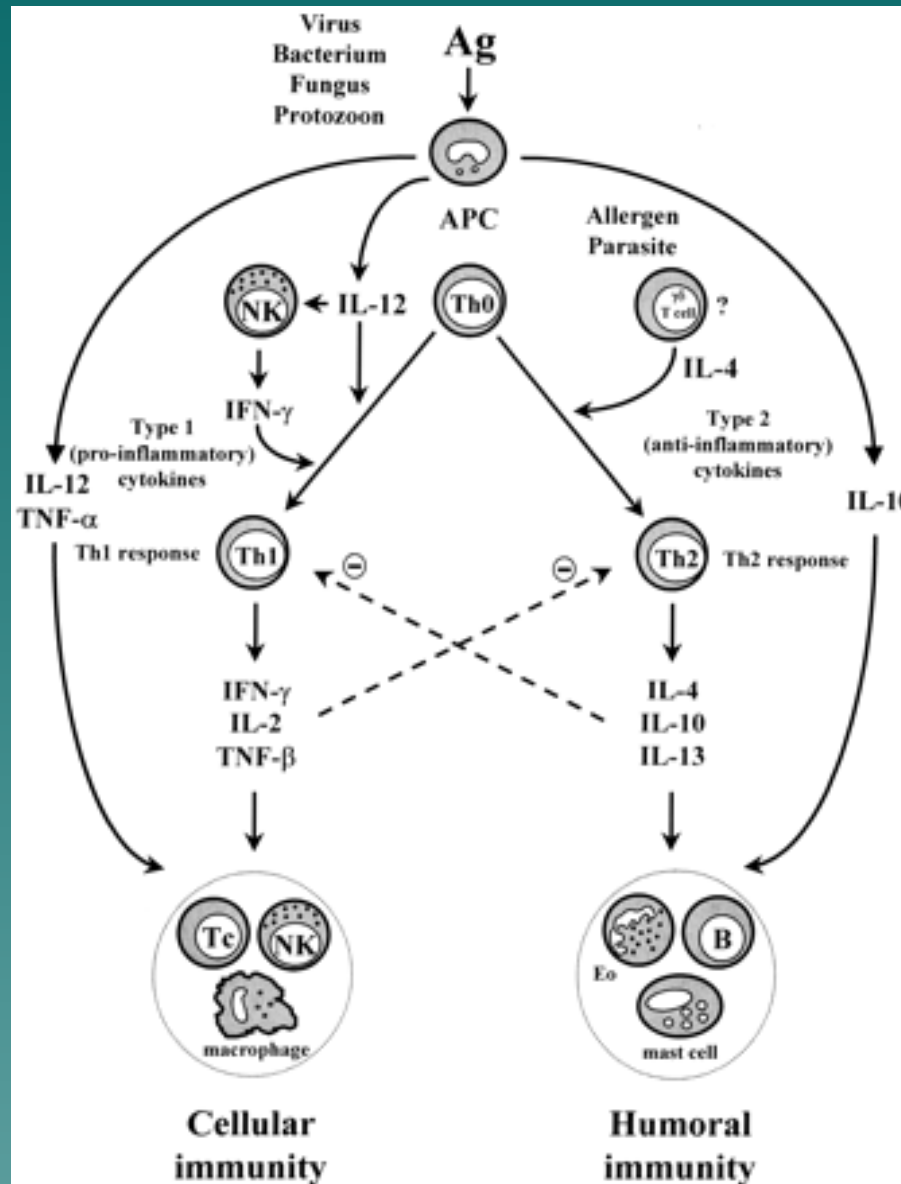
Outline

- ◆ Immune system
- ◆ Echinacea
- ◆ Vitamin E
- ◆ Zinc
- ◆ N-3 fatty acids

Immune System During Aging

- ◆ Innate immunity (rapid)
 - Neutrophils
 - NK
 - M ϕ
 - DC
- ◆ Adaptive Immunity (delayed)
 - T cells
 - B cells
 - DC
- ◆ Breakdown of immunological tolerance and changes in co-stimulatory molecules and cytokines may cause diseases of aging

Role of APCs, Th1 and Th2 cells, and proinflammatory and antiinflammatory cytokines in the regulation of cellular and humoral immunity.



Cytokines in Autoimmune Disease

- ◆ Cellular immunity

Th-1 cytokines (IL-2, IFN- γ) initiate organ-specific autoimmune diseases (IDDM, thyroiditis, MG, SS, gastritis, etc.)

- ◆ Humoral immunity

Th-2 cytokines (IL-4, IL-10, IL-13, etc.) initiate systemic autoimmune diseases (RA, SLE, MS, scleroderma, etc.)

Echinacea

◆ Species

- *E. angustifolia*
- *E. pallida*
- *E. purpurea*

- ◆ Used by native Americans for many centuries mostly for pain relief, coughs, sore throats, fevers, infection, arthritis, antidote for snake poisons, etc.

Products

- ◆ Different parts of the plants – roots
- ◆ Active ingredients
 - Polysaccharides
 - Glycoproteins
 - Alkanamides
 - Flavonoids
- ◆ Pharmacologic action
 - Stimulates immunity
 - Wound healing
 - Anti-inflammatory
 - anti-viral and anti-fungal
 - Local anesthetic
 - Upper respiratory tract infection
 - Cold prevention

Overall Findings

- ◆ Helpful in treatment or prevention of upper respiratory tract infection
- ◆ Increases cytokine production in macrophages
 - TNF- α
 - IL-1
 - IL-6
- ◆ Data from 16 randomized trials so far are not fully convincing – may be related to:
 - Product variation
 - Adulteration
- ◆ Side effects minimum (not fully studied)
- ◆ 900-1000 mg 3X/day or liquid form

Recommendations

- ◆ Need to test good quality products in young and old animals to compare:
 - changes in cellular and humoral immune function,
 - changes in cytokine production and mRNA levels.
- ◆ IF results are favorable then need clinical trials.

Vitamin E

- ◆ Abundant in seed oils (soybean, safflower) and corn and nuts
- ◆ Among natural tocopherols, α -tocopherol (R,R,R-tocopherol) is much higher than β , γ , or δ .
- ◆ One international unit (IU) of vitamin E is referred to as 1 mg of the synthetic form: all-rac- α -tocopheryl acetate (formerly dl- α -tocopheryl acetate)

Vitamin E

- ◆ Is a fat-soluble antioxidant
- ◆ Acts as an antioxidant and free radical scavenger
- ◆ Enhances the immune system
- ◆ Prolongs red blood cell function
- ◆ Increases metabolism of PUFA
- ◆ Increases synergy with vit. C, A, and selenium
- ◆ RDA is 15 mg/d for men and women

Role of Vitamin E Supplement in Elderly

- ◆ Enhances lymphocyte proliferation
- ◆ Increases IL-2 production
- ◆ Increases delayed type hypersensitivity (DTH) skin response
- ◆ Decreases NO and COX-II activity and PGE₂ production
- ◆ High levels (200-800 mg/d) increase T cell function in healthy elderly
- ◆ Variable results with 100 IU levels

Vitamin E Decreases Heart Disease and Cancer

- ◆ Vitamin E (100-400 IU) decreased coronary heart disease and mortality
- ◆ Vitamin E (50-200 IU/day) decreased colon cancer and prostate cancer (Ames, 2001)
- ◆ Vitamin E is essential for genome stability and to reduce DNA damage (Meydani, 2001)

Role of γ -Tocopherol

- ◆ Deserves more attention
- ◆ Ames group: Am J Clin Nutr 74:714, 2001
 - May act far more effectively against CVD and cancer than α -tocopherol
 - Role during aging is less known – particularly in immune function
 - Need new studies to compare the antioxidant potency and immune enhancing capacity of α & γ -tocopherols

Future Directions

- ◆ Need dose response studies with 100-400 IU in healthy subjects and elderly subjects with chronic diseases or frailty because the present RDA (10-15 mg) may be too low for restoring immune function.
- ◆ Need both molecular and immunological studies with and without α and γ -tocopherol supplements to assess DNA damage and Th-1 and Th-2 cytokines and incidence of various diseases.

Zinc Deficiency could occur in the elderly due to:

- ◆ Chronic malnutrition
- ◆ Chronic alcoholism
- ◆ Chronic digestive disorders
- ◆ Long-term vegetarian diets
- ◆ Need to avoid zinc toxicity

Role of Zinc in Immune Response

◆ Essential for:

- cell replication – stimulates >100 enzymes
- cell cycle of lymphocytes (G1, G2, M, and S phase)
- Lymphocyte activation (T-lymphocytes and signal transduction)
- Apoptosis (thymic atrophy)
- Antioxidant activity
- Th-1 cytokines, B-cell development, and IgG production

Zinc Deficiency in the Elderly May Cause:

- ◆ Immune deficiency of T and B cells
- ◆ Deficient phagocytic function
- ◆ Increased skin and respiratory infections and decreased wound healing
- ◆ Decreased taste and smell
- ◆ Increased esophageal cancer
- ◆ 18% of US population consumes less than ½ RDA of Zinc (8 mg/d for women, 11 mg for men – max 40 mg/d)

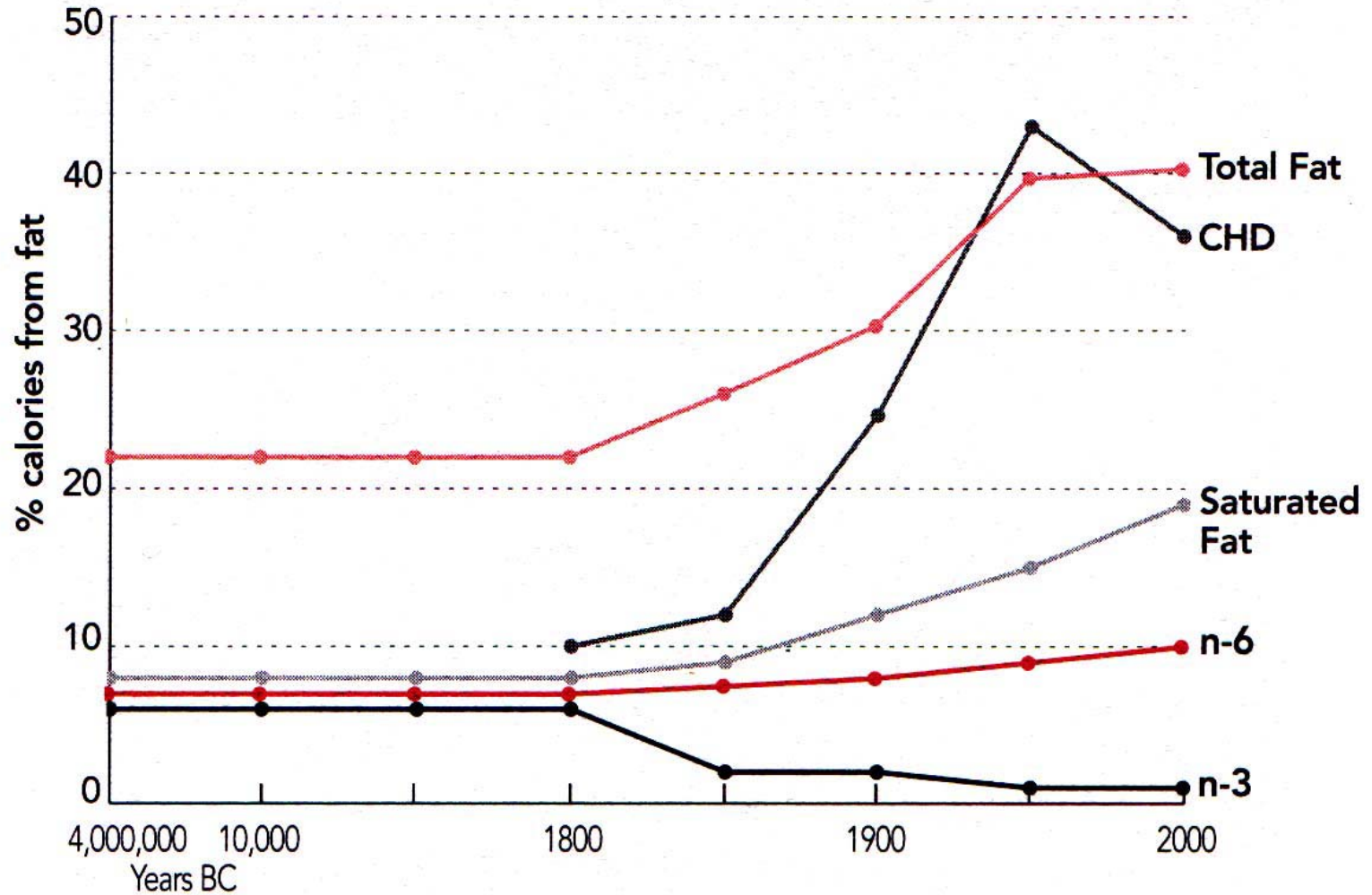
Future Research

- ◆ Need to measure serum zinc levels in healthy vs. frail elderly or subjects with chronic autoimmune disorders or RA
- ◆ Clinical trials with zinc supplements – dose response studies to measure
 - Immune function
 - Th-1 and Th-2 cytokines
 - Response to vaccines, flu attacks and other infection episodes

Role of N-3 Fatty Acids

- ◆ Essential for nervous system in infants
- ◆ Inhibits coronary artery disease (hypertension, hyperlipidemia)
- ◆ Inhibits inflammatory diseases (autoimmune diseases, arthritis)
- ◆ May inhibit some cancers (colon, prostate, breast, etc.)
- ◆ May inhibit skin disorders, asthma, diabetes, chronic depression

Fat Intake and Incidence of Coronary Heart Disease⁹



Salem, N. Jr., 1999

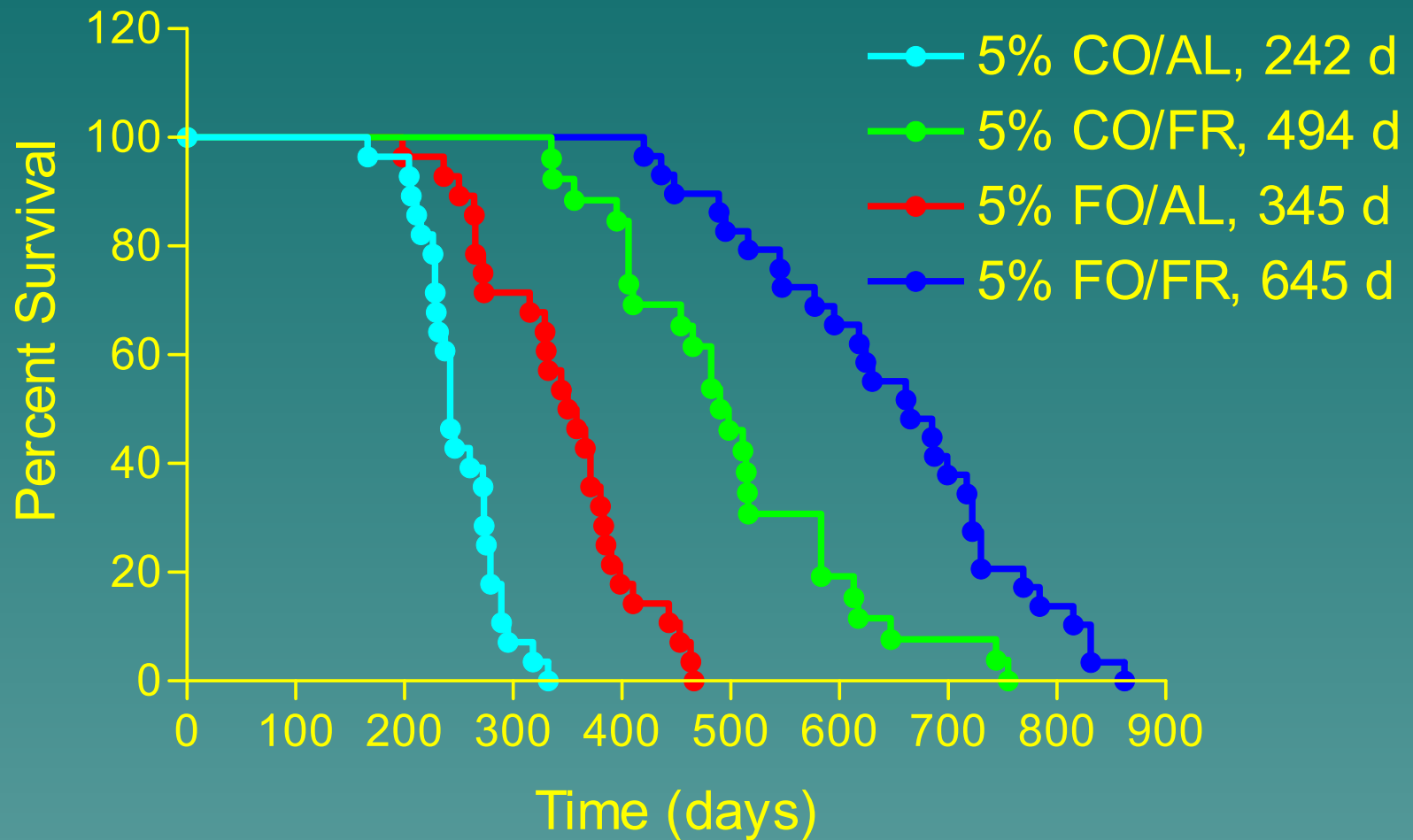
Consequences of Excess and Unbalanced Fat Intake

- ◆ Early puberty
- ◆ Obesity
- ◆ Diabetes
- ◆ Heart Disease
- ◆ Cancer
- ◆ Kidney Disease
- ◆ Infection, etc.

Studies on n-3 fatty acid effects in inflammatory diseases in humans

Disease	# of Studies	Benefits
Coronary Heart Disease	23	Decreased CVD mortality and myocardial infarction
Rheumatoid Arthritis	21	Decreased pain, CRP, NSAID medications
Crohn's Disease	7	Decreased PGE ₂ , TXB ₂ , rate of relapse
Ulcerative Colitis	10	Decreased disease activity, prednisone dose
Osteoporosis	3	Increased osteocalcin, bone density, serum CA

Effect of fish oil and calorie restriction on survival of lupus prone B/W mice (n=28)



Molecular and Immune Mechanisms Involved in the Therapeutic Effects of n-3 Fatty Acids

- ◆ Inhibition of pro-inflammatory cytokines, IL-1, IL6, TNF- α
- ◆ Inhibition of T-cell function
- ◆ Inhibition of COXII & PGE₂
- ◆ Inhibition of free radicals
- ◆ Increased antioxidant enzymes
- ◆ Altered gene expression

Number of Genes with Expression Altered by Fish Oil Feeding (compared to n-6 oil)

◆ Increased

- Immune reaction - 4
- Fat oxidation - 4
- Antioxidant - 5

◆ Decreased

- Cholesterol & fatty acid synthesis - 6
- Transcription - 5
- RO and PPAR α activator production - 3

Current ω -3 intakes in the US compared with Recommendations

PUFAs	Current US Consumption, g/d	Expert US Panel Recommended g/d	British Nutr Foundation Recommended g/d
ALA (18:3)	1.4	2.2	2.4
EPA (20:5), DHA (22:6)	0.1 – 0.2	0.65	1.2
Total	1.6	2.85	3.6

Fatty Acid Composition of Oils (%) Needing Testing in the Elderly

	Crude		Deodorized Fish Oils				
Fatty Acid	Corn Oil	MO n-3	OP n-3	18/12 n-3	30/20 n-3	50/5 n-3	5/50 n-3
Sat	13.1	33.2	35.1	23.5	4.23	6.55	2.6
MUFA	28.0	28.7	28.2	21.3	13.93	14.1	8.0
N-6	56.1	11.4	12.0	13.8	19.81	15.8	12.1
N-3	1.3	26.7	24.6	41.4	62.02	63.6	77.3
Vit E (µg/ml)	230	N.D.	477	330	411	323	295

Future Research

- ◆ Need to undertake multi-center n-6 and well-defined n-3 fatty acid supplement studies in large numbers of healthy vs chronically ill or frail elderly subjects to measure:
 - Lipid profiles
 - Disease symptoms
 - Immune parameters
 - Cytokines/eicosanoids
 - Antioxidants/free radicals
 - Osteoporosis/arthritis

In Summary

- ◆ Dietary supplement need and dosage may vary among the following elderly
 - Healthy and active
 - Overweight and obese
 - Inactive with chronic illness
 - Cognitive and functional decline with frailty
- ◆ Need to consider the diet/caloric intake and physical activity/exercise along with well-defined DS to maintain optimal immune function for healthy aging

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