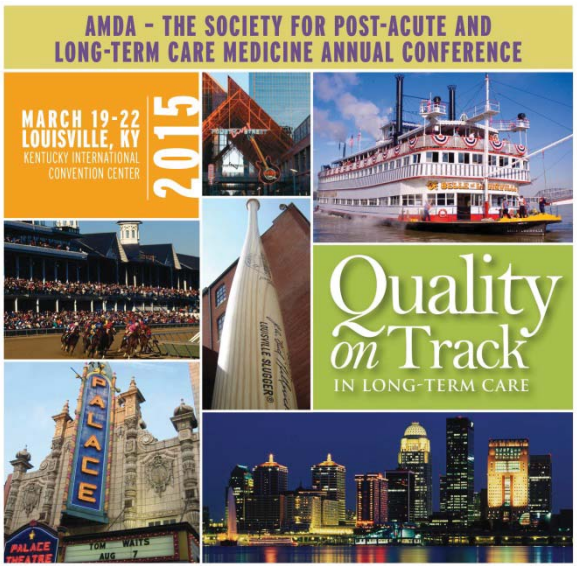
A33 - Vitamins or No Vitamins

Thursday, March 19
8:00 AM - 11:30 AM



Session Description
This session will describe the pathophysiology of vitamins and their role in disease prevention. We will use a case-based approach to discuss vitamin deficiencies and appropriate replacement options. We will also discuss the dangers of using megadoses of vitamins and vitamin-drug interactions. We will discuss, if with adequate nutrition, it is necessary to replace vitamins, and if so which ones.

Learning Objectives

- Describe the physiological role for vitamins.
- Discuss vitamin deficiency syndromes and how to recognize them in the clinical setting.
- Explain abuse of vitamins and the adverse effects of hypervitaminosis.
- Discuss the role of vitamin supplementation in the post-acute long-term care setting.

Presenter(s): Suzanne C. Cryst, RD, CSG, LD; T.S. Dharmarajan, MD; Meenakshi Patel, MD, MMM, CMD; Naushira Pandya, MD, CMD

Presenter(s) Disclosures: All speakers have reported they have no relevant financial relationships to disclose.

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The Society for Post-Acute and Long-Term Care Medicine

Vitamins or No Vitamins?

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Speaker Disclosures

Suzanne has disclosed that she has no relevant financial relationship(s).

Learning Objectives

By the end of the session, participants will:

- Have knowledge of vitamin rich food sources, functions, effects of deficiency/toxicity.
- Understand the objectives of menu planning to aide in meeting nutritional needs
  - Food first
  - Fortified meal plan
- Identify the role of the comprehensive assessment

FAT SOLUBLE VITAMINS ADEK

Vitamin A Foods

- Sources - As preformed vitamin: fish, liver oils, liver, egg yolks, butter, vitamin A fortified dairy products. As provitamin carotenoids: dark green and yellow vegetables, yellow and orange fruits
- Function – Formation of rhodopsin (a photoreceptor pigment in the retina). Integrity of epithelia. Lysosome stability. Glycoprotein synthesis.
- Deficiency – Night blindness
- Toxicity – Headache, bone thickening, hypercalcemia

Vitamin D Foods

- Sources – Fortified dairy products is main dietary source, fish, liver oils, fatty fish, liver
- Functions – Calcium and phosphate absorption. Mineralization and repair of bone. Tubular reabsorption of Calcium, Insulin and thyroid function, improvement of immune function, reduce risk of autoimmune disease
- Deficiency – Osteomalacia, rickets
- Toxicity – Hypercalcemia, anorexia, renal failure, metastatic calcifications

Vitamin E Foods

- Sources – Vegetable oils, nuts, legumes
- Functions – Intracellar antioxidant.
- Deficiency – RBC hemolysis, neurologic deficits

Vitamin K Foods

- Sources – Green leafy vegetables (especially collards, spinach, dark salad greens), soy beans, vegetable oils.
- Functions – Formation of prothrombin, other coagulation factors, and bone proteins
- Deficiency – Bleeding due to deficiency if prothrombin and other factors, osteopenia

WATER SOLUBLE VITAMINS

- B Vitamins
  - Folate (folic acid)
  - Niacin (nicotinic acid, nicotinamide)
  - Riboflavin (B2)
  - Thiamin (B1)
  - B6 (pyridone, pyridoxal, pyridoxamine)
  - B12 (cobalamins)
- Vitamin C (ascorbic acid)

Folate

- Sources – fresh green leafy vegies, fruits, organ meats, enriched cereals and breads
- Functions – Maturation of RBC. Synthesis of purines, pyrimidines, methionine
- Effects of Deficiency/Toxicity – Megoblastic anemia, confusion

Niacin

- Sources – Liver, red meat, fish, poultry, legumes, whole-grain/enriched cereals and breads
- Function – Carbohydrate and cell metabolism. Oxidation – reduction reactions
- Deficiencies – Pellagra (dermatitis, glossitis, GI and CNS dysfunction)
- Toxicity - Flushing

Riboflavin

- Sources – Milk, cheese, liver, meat, eggs, enriched cereal products
- Functions – Many aspects of carbohydrate and protein metabolism
- Deficiency – Cheliosis, angular stomatitis, corneal vascularization

Thiamine

- Sources – Whole grains, meats (especially pork and liver), enriched cereal products, nuts, legumes, potatoes.
- Functions – Carbohydrate, fat, amino acid, glucose and alcohol metabolism. Central and peripheral nerve cell function. Myocardial function.
- Deficiency – Peripheral neuropathy, heart failure. Wernicke-Korsakoff syndrome

B6

- Sources – Organ meats, whole grain cereals, fish, legumes
- Functions – Many aspects of nitrogen metabolism, tryptophan conversion to niacin
- Deficiency – Seizure, anemia, neuropathies, seborrheic dermatitis
- Toxicity – Peripheral neuropathy

B12

- Sources – Meats (pork, beef, organ meats), poultry, eggs, fortified cereals, milk/milk products
- Functions – Maturation of RBC's, neural function, DNA synthesis, myelin synthesis and repair
- Deficiency – Megaloblastic anemia, neurological deficits – confusion, paresthesias, ataxia.

Vitamin C – Ascorbic Acid

- Sources – Citrus fruits, tomatoes, potatoes, broccoli, strawberries, sweet peppers.
- Functions – Collagen formation, bone and blood vessel health. Hormone and amino acid formation. Wound healing.
- Deficiency –Scurvy, hemorrhages, loose teeth, gingivitis, bone defects.

MINERALS - CALCIUM

- Sources – Milk, yogurt, cheese. Leafy green vegies, seafood, legumes, fortified food and beverages.
- Functions – Vascular contractions& vasodilation, muscle function, nerve transmissions, hormone secretions.
- Deficiency – Abnormal heart rhythms, numbness and tingling fingertips, muscle cramps, poor appetite, lethargy

Menu Development

- "Guidelines" provided in regulatory process to meet minimum requirements for standard menu
  - Protein
  - Milk Sources
  - Vitamin C
  - Vitamin A
  - Energy, Carbohydrates, Bread, Cereals
  - Fruits/Vegetables
  - Fluids

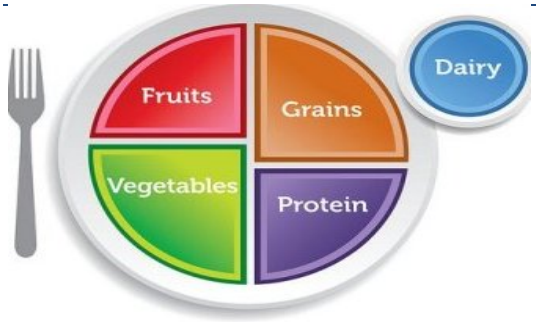
Menu Development - continued

- Reflect food preferences
- Adequate personnel with skills to prepare and serve
- Equipment available
- Flavor variety
- Consistency- combination of soft and crisp

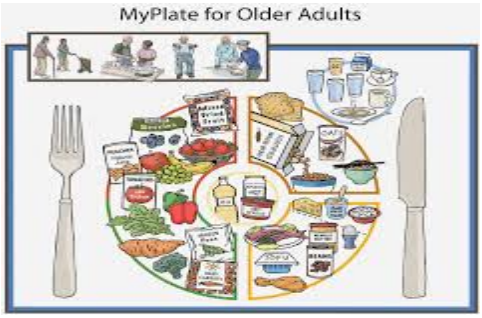
Menu Development - continued

- Texture – variety of ground, chopped and whole
- Color
- Variety
  - Functional foods
  - Fortified Foods
  - Whole grains
- Budget
  - Maximize every penny and Every Bite

My Plate 2015



My Plate for Older Adults – Tufts University



Comprehensive Assessment

- Anthropometric Measures
- Physical Assessment
- Lab Data
- Diagnosis
  - Nutrition related
  - Other

Comprehensive Assessment - continued

- Collaboration with the IDT
- Plan of Care
  - Food First
  - Supplementation – food or medication type

Comprehensive Assessment - continued

- Monitor and Evaluation
  - Continue current plan
  - Issue resolved
  - Make changes in plan of care and continue on

Conclusion

- Accurate Assessment is Vital
- Collaboration with IDT is a focus
- Food First is preferred
- Vitamin usage – document need and outcomes

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- Matarese L., et.al. Gastrointestinal Nutrition, Academy of Nutrition and Dietetics, 2015
- Chernoff R, Ed. Geriatric Nutrition, 2014.
- Niedert KC, Dorner B, Eds. Nutrition Care of the Older Adult: A Handbook for Dietetics Professionals Working throughout the Continuum of Care / Edition 2. 2004 Academy of Nutrition and Dietetics. New issue in October 2015
- Nutritional Disorders. www.merckmanuals.com/professional. Accessed January 14,2015.

Vitamins or NO Vitamins

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Speaker Disclosures

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Research Support

Accera; Avanir; Elan; Forest; Lundbeck; Novartis; Otsuka; Merck; Janssen; Eli Lilly; Avid; Astra Zeneca; GSK

Speaker

Forest; Boehringer Engelheim; Avanir; Sanofi; GSK

Learning Objectives

By the end of the session, participants will be able to:

- **Learning Objective 1**
- Discuss physiological role for vitamins
- **Learning Objective 2**
- Understand vitamin deficiency syndromes and how to recognize them in the clinical setting
- **Learning Objective 3**
- Become familiar with abuse of vitamins and the adverse effects of hypervitaminosis
- **Learning Objective 4**
- Discuss the role of vitamin supplementation in the post-acute long-term care setting

VITAMIN A

Vitamin A is a generic term for many related compounds.

Retinol (alcohol), Retinal (aldehyde) are often called preformed vitamin A. Retinal can be converted by the body to retinoic acid which is known to affect gene transcription.

Body can convert b-carotene to retinol, thus called provitamin A.

FUNCTIONS

•Vision: integrity of eye & formation of rodopsin necessary for dark adaptation.

•Regulation of gene expression: vital to cell differentiation & physiologic processes

•Immunity: important for activation of T lymphocyte, maturation of WBC & integrity of physiological barrier.

•Growth & development

Nutrient Interactions

Zinc deficiency interferes with vitamin A metabolism in several ways:

✓It decreases the synthesis of retinol binding protein, which transports retinol to tissues.

✓It decreases the activity of the enzyme retinyl palmitate, which is necessary for release of retinol from the liver.

✓Zn is needed for the enzyme that convert retinol into retinal.

Nutrient Interactions/2

Iron & vitamin A.

- ✓**Vitamin A deficiency may exacerbate Iron Deficiency Features**
- ✓**Vitamin A supplementation improves iron status among children & pregnant women.**
- ✓**Combining vitamin A with iron controls Iron Deficiency anemia more quickly & effectively than using iron alone.**

VITAMIN A UNITS

1 μg of retinol = 6 μg of β-carotene.

3 μg of retinol = 10 international units of vitamin A.

100 mg carrots contain 10 mg of β-carotene.

Recommended Allowance

Life stage	μg/day
Infants	400-500
Children	300-600
Adolescent	900M- 700F
Adult	900M- 700F
Pregnant women	750-800
Lactating women	122-1300

CASE 1

An older Nursing home adult has had several falls. He has poor vision due to cataracts. He has adequate food intake and some cognitive deficits but is cooperative.

His family brings in a large number of supplements and insists that he take them.

Case 1 (continued)

What is most likely to help reduce his risk of falls?

1. Supplement Vitamin A in recommended doses daily
2. Supplement Vitamin A with Vitamin D in recommended doses daily
3. Avoid supplements other than Vitamin D as long as he eats regular meals
4. Provide a multivitamin that incorporates all essential vitamins discouraging intake of all additional supplements

Vitamin A Intakes and Status

NHANES 2007-2008 Data

Adult men average 649 mcg RAE[1]

Adult Women average 580 mcg RAE

Groups at risk in adults:

Cystic fibrosis[2]

Vegetarians

Alcoholics

Liver impairment

Crohns disease

Overall adults are rarely Vitamin A deficient and don't need supplements

1.Ross A. Vitamin A and Carotenoids. In: Shils M, Shike M, Ross A, Caballero B, Cousins R, eds. Modern Nutrition in Health and Disease. 10th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2006:351-75.

2.O'Neil C, Shevill E, Chang AB. Vitamin A supplementation for cystic fibrosis. Cochrane Database Syst Rev 2010:CD006751.pub2

Vitamin A Deficiency

Night Blindness and Xerophthalmia

Low iron status and Anemia

Increases severity and mortality of infections (esp. diarrhea and measles)

Growth retardation

1. Ross CA. Vitamin A. In: Coates PM, Betz JM, Blackman MR, et al., eds. Encyclopedia of Dietary Supplements. 2nd ed. London and New York: Informa Healthcare; 2010:778-91
2. World Health Organization. Global Prevalence of Vitamin A Deficiency in Populations at Risk 1995–2005. WHO Global Database on Vitamin A Deficiency Geneva: World Health Organization 2009
3. Sommer A. Vitamin A deficiency and clinical disease: An historical overview. J Nutr 2008;138:1835-9

Vitamin A and Cancer

Lung Cancer:

ATBC[1] and CARET[2] studies:

Smokers/exposure to asbestos and those taking very high dose beta carotene with or without retinal palmitate –

Increased risk of lung cancer

Physicians Health Study[3]:

No assoc. of high dose with cancer risk ? only 11% physicians smokers

1.The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029-35
2. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996;334:1150-5
3. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. The New England journal of medicine 1996;334:1145-9.

Vitamin A and Cancer

Prostate Cancer:
ATBC[1] :

Baseline beta-carotene levels no effect on survival
Highest quintile 20% more likely to develop prostate cancer compared to lowest quintile

CARET[2] :

Those who took daily supplements of Beta carotene 35% lower risk of Non aggressive prostate cancer compared to those who didn't

1.Watters JL, Gail MH, Weinstein SJ, Virtamo J, Albanes D. Associations between alpha-tocopherol, beta-carotene, and retinol and prostate cancer survival. Cancer Res 2009;69:3833-41
2. Mondul AM, Watters JL, Mannisto S, Weinstein SJ, Snyder K, Virtamo J, et al. Serum retinol and risk of prostate cancer. Am J Epidemiol 2011;173:813-21.
3. Neuhouser ML, Barnett MJ, Kristal AR, Ambrosone CB, King IB, Thornquist M, et al. Dietary supplement use and prostate cancer risk in the Carotene and Retinol Efficacy Trial. Cancer Epidemiol Biomarkers Prev 2009;18:2202-6

Macular Degeneration (AMD)

Age-related eye disease study (AREDS)[1]:

Decreased risk of advanced AMD by 25% in those taking 15 mg beta carotene with Vitamins C and E and Zn and Selenium

AREDS-2 follow up study[2]:

Same protection with or without beta carotene in the supplement
18% lower risk in those taking lutein and zeaxanthin compared to those taking beta Carotene

1. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001;119:1417-36.
2. The Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA 2013;309:2005-15

Health Risks from Excess Vitamin A

Hypervitaminosis A leads to:

Pseudotumor Cerebri
Headaches
Dermatitis with Xanthosis Cutis
Bone pain and increased risk of fracture
Coma
Death

1. Ross CA. Vitamin A. In: Coates PM, Betz JM, Blackman MR, et al., eds. Encyclopedia of Dietary Supplements. 2nd ed. London and New York: Informa Healthcare; 2010:778-91
2. Solomons NW. Vitamin A. In: Bowman B, Russell R, eds. Present Knowledge in Nutrition. 9th ed. Washington, DC: International Life Sciences Institute; 2006:157-83.
3. Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc Washington D.C. National academy 2001

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Health Risks from Excess Vitamin A

Beta Carotene in excess leads to:

- Carotenodermia[1]
- Increased risk of lung Cancer[2]
- Increased cardiovascular mortality[3]

•1.Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids Washington, DC: National Academy Press; 2000
•2.The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029-35
•3. The Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA 2013;309:2005-15

THERAPEUTIC USES

Vitamin A deficiency

Boosting immunity of infants

Skin disorders

Acute promyelotic leukemia

Cancer prevention (lung & breast)

Fig. 6-1 Follicular hyperkeratosis in vitamin A deficiency.

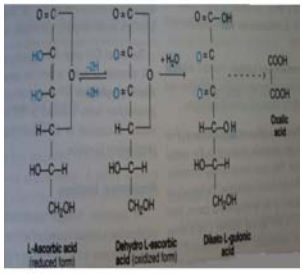
From "Fundamentals of Clinical Nutrition" by R. L. Weinsier copyright 1993 by Mosby-Year Books N.Y.

VITAMIN C

- Water soluble vitamin.
- Acts as anti-oxidant.
- Vit.C necessary for a number of metabolic processes including H2 ion transfer and maintenance of intracellular redox potential.
- Facilitates uptake of iron in intestinal tract.
- Involved in formation of active form of folic acid (folinic acid)
- Highly concentrated in the pituitary, adrenals, eyes, platelets and WBCs.

STRUCTURE

- Hexose derivative.
- Acidic property of due to enolic hydroxyl groups.
- Strong reducing agent in aq. Phase of living tissues
- Easily and reversibly oxidised to dehydroascorbic acid
- Oxidation of Vit.C rapid in presence of copper, hence inactivated if food prepared in copper vessels.



BIOSYNTHESIS AND METABOLISM

- Many animals synthesize ascorbic acid from glucose via uronic pathway.
- Man and other primates cannot synthesize Vit.C due to the lack of single enzyme l-gluconelactone oxidase.
- Dependence on dietary sources.
- Its very easily destroyed by heat, increased ph and light and is very soluble in water.

RECOMMENDED DIETARY ALLOWANCE (RDA)

- The recommended dietary allowance for Vit.C ranges from 35mg in infants to 60mg in adults.
- Pregnant and lactating women should increase their intake by 20mg and 40mg respectively

FUNCTIONS OF VITAMIN C

- Collagen formation
- Anti-oxidant
- Bone formation
- Various metabolic pathways
- Synthesis of corticosteroid hormone
- Immunologic function

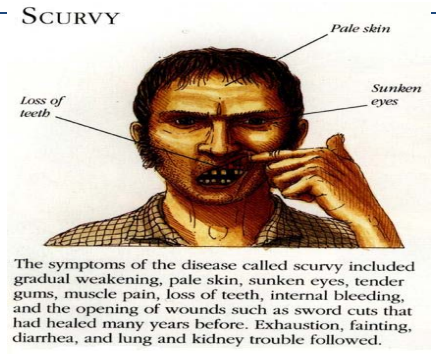
EXCRETION

- Vit.C is a threshold substance and is excreted primarily through kidney.
- Degree of tissue saturation determines the amount excreted.
- If intake is normal, slight increase in intake above normal will be excreted.
- If tissues are un-saturated through low intake or excess metabolism of vit.C even high doses may be retained

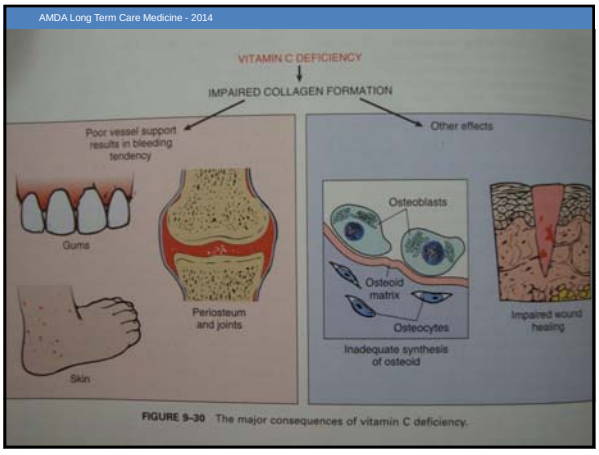
CLINICAL FEATURES OF VIT.C DEFICIENCY IN ADULTS

- Perifollicular hemorrhages
- Gum involvement
- Cork screw hair appearance
- Petechial hemorrhages
- Ecchymosis anywhere on the body
- Hemorrhages may occur into nerve sheath, joints, GI tract
- Epistaxis may occur
- Delayed wound healing
- Normocytic normochromic anemia

CLINICAL MANIFESTATIONS



The symptoms of the disease called scurvy included gradual weakening, pale skin, sunken eyes, tender gums, muscle pain, loss of teeth, internal bleeding, and the opening of wounds such as sword cuts that had healed many years before. Exhaustion, fainting, diarrhea, and lung and kidney trouble followed.



LONGITUDINAL SECTION OF A COSTOCHONDRAL JUNCTION WITH WIDENING OF EPIPHYSEAL CARTILAGE

Fig 9.3.5 Scurvy: Note the deformity of knee joints produced due to repeated haemorrhage into joints.

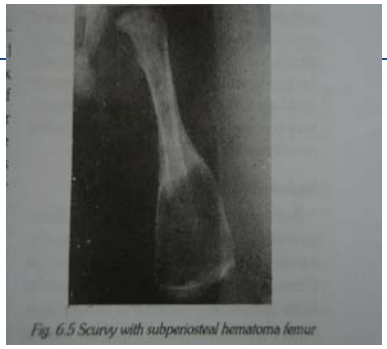


Fig. 6.5 Scurvy with subperiosteal hematoma femur

ORAL MANIFESTATIONS

- Deficiency of vit.C chiefly occurs in gingival and periodontal tissues.

Fig. 2-5 Periodontal disease seen in scurvy.

ORAL MANIFESTATIONS

- The interdental and marginal gingiva is bright red with swollen, smooth, shiny surface.
- In almost all cases of acute or chronic scurvy, the gingival ulcers show the typical organisms and patients have typical foul breath of persons with fusospirochetal stomatitis.
- In the severe chronic cases of scurvy, hemorrhages and swelling of periodontal membranes occur, followed by loss of bone and loosening of teeth which eventually exfoliate.

HISTOLOGIC FEATURES

- In scurvy, osteoblasts fail to form osteoid to lay down on the spicules of calcified cartilage matrix.
- This spicules are nonresistant to weight bearing and motion stresses so they are liable to fracture. They lead to characteristic lesions in skeleton in scurvy.
- As the lattice increases in width, more fragile zone develops, so that complete fracture of spicules occur with the separation and deformity of cartilage shaft junction
- Sub periosteal hemorrhages are frequent in scorbutic animals.

PREVENTION AND TREATMENT

- **Mother's milk and proprietary milk preparations are good source vitamin.C**
- **Old and solitary patients should be given 50mg of vitamin C daily.**
- **Adequate amount of Vit.C should be given to patient during trauma, surgery, burns, infections, smoking and during administration of aspirin, tetracyclins, steroids and indomethacin.**
- **For treatment, 250mg Vit.C 8-hourly by mouth should saturate the tissues quickly.**
- **If patient is anemic, iron and folic acid are also indicated**

Groups at Risk For Deficiency

- Smokers
- Infants fed Evaporated or Boiled Milk
- Monotonous Diets
- Alcohol and Drug abuse
- Elderly
- Intestinal malabsorption syndromes
- Cancer
- ESRD/Chronic Hemodialysis

Cancer Prevention

Mixed results

- Reduces formation of carcinogens like nitrosamines[1]
- Works as an antioxidant-prevents oxidative damage that can lead to cancer[2]
- Enhances immune response[3]
- Cancer patients have lower level of Vitamin C[4]

1. Hecht SS. Approaches to cancer prevention based on an understanding of N-nitrosamine carcinogenesis. Proc Soc Exp Biol Med 1997;216:181-91
2.Jacob RA, Sotoudeh G. Vitamin C function and status in chronic disease. Nutr Clin Care 2002;5:66-74
3. Li Y, Schellhorn HE. New developments and novel therapeutic perspectives for vitamin C. J Nutr 2007;137:2171-84
4. Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. Am J Clin Nutr 1999;69:1086-107

Cancer Prevention

Mixed results

- Nurses Health Study: Highest intake (203 mg/day average) 63% lower risk of breast cancer compared to lowest intake (70mg/day average) in premenopausal women with family history of breast cancer[1]
- Kushi and colleagues: Highest intake (198 mg/day average) no difference in risk of breast cancer compared to lowest intake (87mg/day average) in postmenopausal women[2]

1. Zhang S, Hunter DJ, Forman MR, Rosner BA, Speizer FE, Colditz GA, et al. Dietary carotenoids and vitamins A, C, and E and risk of breast cancer. J Natl Cancer Inst 1999;91:547-56

2. Kushi LH, Fee RM, Sellers TA, Zheng W, Folsom AR. Intake of vitamins A, C, and E and postmenopausal breast cancer. The Iowa Women's Health Study. Am J Epidemiol 1996;144:165-74

Cancer Prevention

Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study

Randomized, double-blind, placebo-controlled clinical trial

13,017 healthy French adults received antioxidant supplementation with 120 mg ascorbic acid, 30 mg vitamin E, 6 mg beta-carotene, 100 mcg selenium, and 20 mg zinc, or placebo [1].

After a median follow-up time of 7.5 years, antioxidant supplementation lowered total cancer incidence in men, but not in women.

- 1. Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, et al. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. Arch Intern Med 2004;164:2335-42

Cancer Prevention

- Supplements of 500 mg/day vitamin C plus 400 IU vitamin E every other day for a mean follow-up period of 8 years failed to reduce the risk of prostate or total cancer compared with placebo in middle-aged and older men participating in the Physicians' Health Study II[1]
- In the Women's Antioxidant Cardiovascular Study Compared with placebo, supplementation with vitamin C (500 mg/day) for an average of 9.4 years had no significant effect on total cancer incidence or cancer mortality[2]

1. Gaziano JM, Glynn RJ, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA 2009;301:52-62
2. Lin J, Cook NR, Albert C, Zaharris E, Gaziano JM, Van Denburgh M, et al. Vitamins C and E and beta carotene supplementation and cancer risk: a randomized controlled trial. J Natl Cancer Inst 2009;101:14-23

Cancer Prevention

- In a large intervention trial conducted in Linxian, China, daily supplements of vitamin C (120 mg) plus molybdenum (30 mcg) for 5–6 years did not significantly affect the risk of developing esophageal or gastric cancer[1]
- 10 years of follow-up, failed to significantly affect total morbidity or mortality from esophageal, gastric, or other cancers[2]
- A review by Coulter and colleagues found that vitamin C supplementation, in combination with vitamin E, had no significant effect on death risk due to cancer in healthy individuals[3]

- 1. Taylor PR, Li B, Dawsey SM, Li JY, Yang CS, Guo W, et al. Prevention of esophageal cancer: the nutrition intervention trials in Linxian, China. Linxian Nutrition Intervention Trials Study Group. Cancer Res 1994;54(7 Suppl):2029s-31
- [2] Qiao YL, Dawsey SM, Kamangar F, Fan JH, Abnet CC, Sun XD, et al. Total and cancer mortality after supplementation with vitamins and minerals: follow-up of the Linxian General Population Nutrition Intervention Trial. J Natl Cancer Inst 2009;101:507-18
- [3] Coulter I, Hardy M, Shekelle P, Udani J, Spar M, Oda K, et al. Effect of the supplemental use of antioxidants vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cancer. Evidence Report/Technology Assessment Number 75. AHRQ Publication No. 04-E003. Rockville, MD: Agency for Healthcare Research and Quality, 2003

Cancer Treatment

- Studies by Cameron, Campbell, and Pauling suggested high-dose vitamin C has beneficial effects on quality of life and survival time in patients with terminal cancer[1,2]
- A randomized, double-blind, placebo-controlled clinical trial by Moertel and colleagues at the Mayo Clinic —did not support these findings Advanced colorectal cancer Vit C 10 gm daily no difference from placebo[3]

- 1. Cameron E, Campbell A. The orthomolecular treatment of cancer. II. Clinical trial of high-dose ascorbic acid supplements in advanced human cancer. Chem Biol Interact 1974;9:285-315
- [2] Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: prolongation of survival times in terminal human cancer. Proc Natl Acad Sci U S A 1976;73:3685-9
- [3] Moertel CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, Ames MM. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison. N Engl J Med 1985;312:137-41

Cardiovascular Disease

- Evidence from many epidemiological studies suggests that high intakes of fruits and vegetables are associated with a reduced risk of cardiovascular disease[1,2]
- In the Nurses' Health Study, a 16-year prospective study involving 85,118 female nurses, total intake of vitamin C from both dietary and supplemental sources was inversely associated with coronary heart disease risk[3]
- A much smaller study indicated that postmenopausal women with diabetes who took at least 300 mg/day vitamin C supplements had increased cardiovascular disease mortality[4]

1. Ye Z, Song H. Antioxidant vitamins intake and the risk of coronary heart disease: meta-analysis of cohort studies. Eur J Cardiovasc Prev Rehabil 2008;15:26-34
2. Willcox BJ, Curb JD, Rodriguez BL. Antioxidants in cardiovascular health and disease: key lessons from epidemiologic studies. Am J Cardiol 2008;101:75D-86D
3. Osganian SK, Stampfer MJ, Rimm E, Spiegelman D, Hu FB, Manson JE, et al. Vitamin C and risk of coronary heart disease in women. J Am Coll Cardiol 2003;42:246-52
4. Lee DH, Folsom AR, Harnack L, Halliwell B, Jacobs DR Jr. Does supplemental vitamin C increase cardiovascular disease risk in women with diabetes? Am J Clin Nutr 2004;80:1194-200

Cardiovascular Disease

- Prospective British study >20,000 42% lower risk of stroke in the top quartile Vit C levels compared to the bottom[1]
- Physician Health Study Vit C for 5.5 years no difference in Cardiovascular or coronary disease mortality[3]
- 2008 meta-analysis 14 studies 10 yr follow up dietary but not supplemental Vit C inversely related to Coronary heart disease[3]

- [1] Myint PK, Luben RN, Welch AA, Bingham SA, Wareham NJ, Khaw KT. Plasma vitamin C concentrations predict risk of incident stroke over 10 y in 20 649 participants of the European Prospective Investigation into Cancer Norfolk prospective population study. Am J Clin Nutr 2008;87:64-9
- 2. Muntwyler J, Hennekens CH, Manson JE, Buring JE, Gaziano JM. Vitamin supplement use in a low-risk population of US male physicians and subsequent cardiovascular mortality. Arch Intern Med 2002;162:1472-6
- 3. Ye Z, Song H. Antioxidant vitamins intake and the risk of coronary heart disease: meta-analysis of cohort studies. Eur J Cardiovasc Prev Rehabil 2008;15:26-34

Cardiovascular Disease

- WAVE trial 423 women with at least one stenosis antioxidant supplement increased cardiovascular mortality[1]
- Systematic review of Vitamin C no favorable effects on cardiovascular disease[2]
- Linxian trial daily supplement reduced cerebrovascular death by 8%[3]

- [1] Waters DD, Alderman EL, Hsia J, Howard BV, Cobb FR, Rogers WJ, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. JAMA 2002;288:2432-40
- 2. Shekelle P, Morton S, Hardy M. Effect of supplemental antioxidants vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cardiovascular disease. Evidence Report/Technology Assessment No. 83 AHRQ Publication No. 03-E043. Rockville, MD: Agency for Healthcare Research and Quality, 2003
- 3. Qiao YL, Dawsey SM, Kamangar F, Fan JH, Abnet CC, Sun XD, et al. Total and cancer mortality after supplementation with vitamins and minerals: follow-up of the Linxian General Population Nutrition Intervention Trial. J Natl Cancer Inst 2009;101:507-18

Cataracts

- 5 yr prospective study in Japan higher dietary intake reduced risk of cataracts[1]
- Study of >24,500 Swedish women showed increased rate of cataracts in those taking high dose supplements of Vitamin C[2]
- Chinese study 180 mg Vit C supplement 43% lower risk of cataracts than placebo[3]
- AREDS 500 mg Vitamin C supplement no difference in risk of developing cataracts compared with placebo

- [1]Yoshida M, Takashima Y, Inoue M, Iwasaki M, Otani T, Sasaki S; JPHC Study Group. Prospective study showing that dietary vitamin C reduced the risk of age-related cataracts in a middle-aged Japanese population. Eur J Nutr 2007;46:118-24
- [2] Rautiainen S, Lindblad BE, Morgenstern R, Wolk A. Vitamin C supplements and the risk of age-related cataract: a population-based prospective cohort study in women. Am J Clin Nutr. 2010 Feb;91(2):487-93
- [3] Sperduto RD, Hu TS, Milton RC, Zhao JL, Everett DF, Cheng QF, et al. The Linxian cataract studies. Two nutrition intervention trials. Arch Ophthalmol 1993;111:1246-53
- [4] The Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein/zeaxanthin for the treatment of age-related cataract: AREDS2 randomized trial report no. 4. JAMA Ophthalmol 2013. Online May

Age-related Macular Degeneration (AMD)

- AREDS showed 28% lower risk of worsening AMD compared to placebo[1]
- Population based cohort study antioxidant supplement resulted in lower risk of AMD[2]
- 2007 systematic review does not support role for antioxidant supplements including Vitamin C in prevention of AMD[3]

- Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001;119:1417-36
- 2. van Leeuwen R, Boekhoorn S, Vingerling JR, Witteman JC, Klaver CC, Hofman A, et al. Dietary intake of antioxidants and risk of age-related macular degeneration. JAMA 2005;294:3101-7.
- 3 Chong EW, Wong TY, Kreis AJ, Simpson JA, Guymer RH. Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis. BMJ 2007;335:755

Common Cold and Vitamin C

- 2007 Cochrane review of placebo controlled trials using Vitamin C for prevention or treatment of colds No benefit[1]
- People exposed to extreme exercise or cold temperatures saw reduction of cold incidence by 50%[2]
- Prophylactic Vit C in general population of at least 200 mg/day might shorten the duration of a cold[3]

Douglas RM, Hemilä H, Chalker E, Treacy B. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2007;(3):CD000980

2. Wintergerst ES, Maggini S, Hornig DH. Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. Ann Nutr Metab 2006;50:85-94

3. Hemilä H. The role of vitamin C in the treatment of the common cold. Am Fam Physician 2007;76:1111, 1115

Case 2

In a patient who can eat adequately, and has a poorly healing sacral pressure ulcer, what would be the single best choice for management in addition to efforts in relieving pressure?

1. Improve nutritional status by incorporating a balanced diet with adequate protein
2. Vitamin C and Zinc until the ulcer heals
3. Vitamin C 250 mg daily for 6 months
4. Vitamin C 250 mg daily with Zinc supplement for 6 months

Vitamin C and Skin Healing

- Common misconception-
- Supplementation of vitamin C and zinc may assist in the prevention and treatment of pressure ulcers.
- Review of the literature found that there is insufficient evidence to support the routine use of supplemental zinc and/or vitamin C in individuals with adequate nutrition.
- Furthermore, supplemental zinc may produce a number of adverse effects.

- Annals of Long-Term Care: Clinical Care and Aging 2010;18[3]:28-32

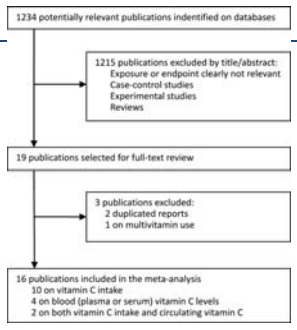
HYPERVITAMINOSIS C

- Postmenopausal women with diabetes >300 mg/day assoc. with increased cardiovascular disease mortality[1]
- Large amounts of iron may be absorbed and may precipitate hemochromatosis.[2]
- Large amounts of oxalate crystals are passed in urine which may precipitate oxalate stone formation.[3]
- Long term use of vit.C may interfere with absorption of vit.B12 hence may cause anemia.

- 1. Lee DH, Folsom AR, Harnack L, Halliwell B, Jacobs DR Jr. Does supplemental vitamin C increase cardiovascular disease risk in women with diabetes? Am J Clin Nutr 2004;80:1194-200
- 2.Institute of Medicine. Food and nutrition board. Washington DC National Academy Press 2000
- 3. Levine M, Rumsey SC, Daruwala R, Park JB, Wang Y. Criteria and recommendations for vitamin C intake. JAMA 1999;281:1415-23.

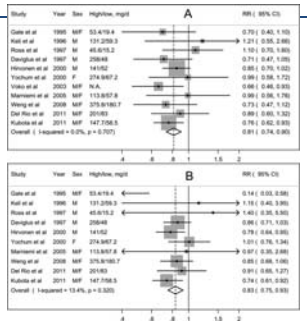
AMDA Long Term Care Medicine - 2014

Flow chart of study selection.



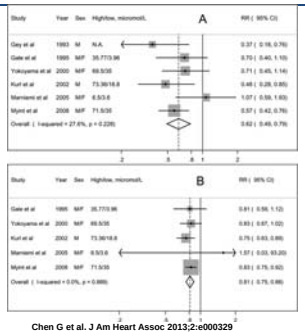
Chen G et al. J Am Heart Assoc 2013;2:e000329

Meta-analysis of dietary vitamin C intake and risk of stroke.



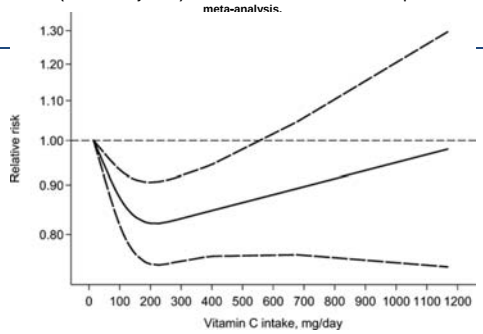
Chen G et al. J Am Heart Assoc 2013;2:e000329

Meta-analysis of circulating vitamin C and risk of stroke.



Chen G et al. J Am Heart Assoc 2013;2:e000329

Relative risk (solid line) with 95% confidence interval (long dashed lines) for the association between vitamin C intake (total or dietary intake) and risk of stroke in a restricted cubic spline random-effects meta-analysis.

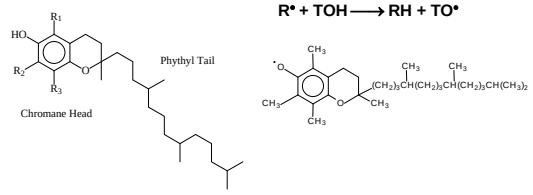


Chen G et al. J Am Heart Assoc 2013;2:e000329

Functions of Vitamin E

- Chain-breaking antioxidant
- Protects cell membranes
- Enhances immune response
- Regulates platelet aggregation
- Regulates protein kinase C activation

Vitamin E as an antioxidant



$R^{\bullet} + TOH \longrightarrow RH + TO^{\bullet}$

	R_1	R_2	R_3
α	CH_3	CH_3	CH_3
β	CH_3	H	CH_3
γ	H	CH_3	CH_3
δ	H	H	CH_3

Absorption and Transport

- Dependent on ability to absorb fat
- Absorbed into lymphatic system
- Component of chylomicrons
- Alpha-tocopherol is major tocopherol in plasma
- Positive association between serum lipid and tocopherol levels
- Normal range is 0.5-1.6 mg/dl

Clinical Deficiency States

- Susceptible groups
  - Patients with malabsorption syndromes
  - Premature infants
  - Patients on TPN
- Characterized by progressive neurological syndrome
  - Gait disturbances
  - Absent or altered reflexes
  - Limb weakness
  - Sensory loss in arms and legs
- Improved neurological function with vitamin E therapy

1. Institute of Medicine. Food and Nutrition Board Washington DC National Academy press 2000
2. Sokoloff KV, Mason JB, Meydani SN, Cornwall S, Grand RJ. Vitamin E deficiency and impaired cellular immunity related to intestinal fat malabsorption. Gastroenterology 1992;102:2139-42

Sources, Intakes and Requirements

- Vegetable oils, sunflower seeds and nuts are the richest dietary sources[1]
- Average daily intake is 15 I.U. in men and 11.4 I.U in women (NHANES III)[2]
- DRI and RDA is 15 mg alpha-tocopherol (22.5 I.U.)
- Optimal vitamin E intakes may be 100-400 I.U. per day

1. U.S. Department of Agriculture, Agricultural Research Service. 2011. USDA National Nutrient Database for Standard Reference, Release 24. Nutrient Data Laboratory Home Page
2. Gao X, Wilde PE, Lichtenstein AH, Bermudez OI, Tucker KL. The maximal amount of dietary á-tocopherol intake in U.S. adults (NHANES 2001-2002). J Nutr 2006;136:1021-6

Efficacy of Natural-Source *vs* Synthetic Vitamin E

- Natural-source is a single isomer (d-alpha-tocopherol)
- Synthetic is a mixture of eight isomers
- Natural-source has twice the bioavailability of synthetic

Protective Role in Disease Prevention

There is extensive evidence implicating oxidative damage in the development of degenerative diseases and conditions.

A number of studies have evaluated the role of vitamin E, alone or in combination with other antioxidants, in preventing or minimizing oxidative damage associated with development of

Cancer,

Coronary heart disease,

Cataracts and

Alzheimer's disease.

Cancer

- Nurses Health Study[1]
- Health Professional Follow up Study[2]
  - No decrease in incidence of Colon Cancer
- Epidemiological study by American Cancer Society[3]
  - Vit E for 10 years or longer reduced risk of mortality from bladder cancer

1. Wu K, Willett WC, Chan JM, Fuchs CS, Colditz GA, Rimm EB, et al. A prospective study on supplemental vitamin E intake and risk of colon cancer in women and men. Cancer Epidemiol Biomarkers Prev 2002;11:1298-304
2. Graham S, Sielezny M, Marshall J, Priore R, Freudenheim J, Brasure J, et al. Diet in the epidemiology of postmenopausal breast cancer in the New York State Cohort. Am J Epidemiol 1992;136:3127-37
3. Jacobs EJ, Henion AK, Briggs PJ, Connell CJ, McCullough ML, Jonas CR, et al. Vitamin C and vitamin E supplement use and bladder cancer mortality in a large cohort of US men and women. Am J Epidemiol 2002;156:1002-10

Cancer

- Intervention trials have shown mixed results
- SELECT trial prospective randomized
  - 5.5 yr follow up No decreased prostate cancer[1]
  - Further 1.5 yr follow up increased risk of cancer compared to placebo[2]
- HOPE-TOO[3]
  - No decrease in number of new cancers
- Womens Health Study[4]
  - No decrease in cancer risk

1. National Cancer Institute. Questions and Answers: Selenium and Vitamin E Cancer Prevention Trial (SELECT).
2. Klein EA, Thompson Jr. IM, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2011;306:1549-1556
3. Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, et al., HOPE and HOPE-TOO Trial Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. JAMA 2005;293:1338-47
4. Lee I-M, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. JAMA 2005;294:56-65

Coronary Heart Disease

- Observational Studies
  - Nurses Health Study[1]
    - 30-40% lower risk of CAD
  - Finnish Study[2]
    - Decreased CHD mortality with Vitamin E

- 1. Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. Vitamin E consumption and the risk of coronary disease in women. N Engl J Med 1993;328:1444-9
- 2. Knekit P, Reunanen A, Jarvinen R, Seppanen R, Heliovaara M, Aromaa A. Antioxidant vitamin intake and coronary mortality in a longitudinal population study. Am J Epidemiol 1994;139:1180-9

Coronary Heart Disease

- RCT
  - HOPE Study[1]
    - No difference in risk of CAD compared to placebo
  - HOPE-TOO[2]
    - No cardiovascular protection
    - 21% increased rate of admission for CHF in Vitamin E grp
  - Women's Angiographic Vitamin and Estrogen Study[3]
    - Increased all cause mortality with Vitamin E
    - No cardiovascular benefit

- 1. Jalal I, Devaraj S. Vitamin E supplementation and cardiovascular events in high-risk patients. N Engl J Med 2000;342:154-60
- 2. Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, et al. HOPE and HOPE-TOO Trial Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. JAMA 2005;293:1338-47
- 3. Waters DD, Alderman EL, Hsia J, Howard BV, Cobb FR, Rogers W-J, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. J Am Med Assoc 2002;288:2432-40

Coronary Heart Disease

- RCT
  - Women's Health Study[1]
    - No difference in risk of CAD compared to placebo
    - 26%decrease non fatal MI; 49% decrease in cardiovascular mortality
  - Physicians Health Study[2]
    - No cardiovascular protection
    - Increased risk for hemorrhagic stroke in Vitamin E grp

- 1. Lee I-M, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. JAMA 2005;294:56-65
- 2. Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. JAMA 2008;300:2123-33

Cataracts

- Vitamin E delayed or minimized cataract development in animal models[1]
- Lens clarity superior with Vitamin E supplement[2]
- Decreased cataract risk associated with vitamin E supplementation[3]
- AREDS and AREDS2 found no relationship with Vitamin E intake in cataract development or progression[4]

- 1. Jacques PF, Taylor A, Moeller S, Hankinson SE, Rogers G, Tung W, et al. Long-term nutrient intake and 5-year change in nuclear lens opacities. Arch Ophthalmol 2005;123:517-26
- 2. Leske MC, Chylack LT Jr, He Q, Wu SY, Schoenfeld E, Friend J, et al. Antioxidant vitamins and nuclear opacities: the longitudinal study of cataract. Ophthalmology 1998;105:831-6.
- 3. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch Opthalmol 2001;119:1439-52
- 4. The Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein/zeaxanthin for the treatment of age-related cataract: AREDS2 randomized trial report no. 4. JAMA Ophthalmol 2013. Online May 5

Age-Related Macular Degeneration (AMD) and Cataracts

- AREDS
  - 25% reduced risk of advanced AMD
  - No effect on progression of cataract
- AREDS 2
  - Reduced progression of AMD over 5 years
  - No effect on cataracts

- 1. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001;119:1417-36
- 2. The Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA 2013;309:2005-15. [PubMed abstract]
- 3. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch Opthalmol 2001;119:1439-52
- 4. The Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein/zeaxanthin for the treatment of age-related cataract: AREDS2 randomized trial report no. 4. JAMA Ophthalmol 2013. Online May 5

Alzheimer's Disease

- Vitamin E or selegiline
  - slowed disease progression in multicenter trial[1]
- Prospective cohort study older men[2]
  - less cognitive decline over 3 years
- MCI trial[3]
  - No difference between Vit E and Placebo
- Trial in older women[4]
  - No cognitive benefits over 4 years

1. Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzehimer's disease. N Engl J Med 1997;336:1216-22
2. Morris MC, Evand DA, Bienias JL, Tangney CC, Wilson RS. Vitamin E and cognitive decline in older persons. Arch Neurol 2002;59:1125-32
3. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352:2379-88
4. Kang JH, Cook N, Manson J, Buring J, Grodstein F. A randomized trial of vitamin E supplementation and cognitive function in women. Arch Intern Med 2006;166:2462-8.

Medication Interactions

- Inhibits platelet aggregation and antagonizes Vit K dependent clotting factors
- Increased risk of bleeding with Coumadin[1]
- Blunts the rise in HDL with Niacin and simvastatin[2]
- Blunt oxidative damage in cancerous cells with chemotherapy[3]

- 1. Natural Medicines Comprehensive Database
- 2. Brown BG, Zhao X-Q, Chait A, Fisher LD, Cheung MC, Morse JS, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 2001;345:1583-92
- 3. Lawenda BD, Kelly KM, Ladas EJ, Sagar SM, Vickers A, Blumberg JB. Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? J Natl Cancer Inst 2008;100:773-83

VITAMINS OR NO VITAMINS?

T.S. Dharmarajan MD, MACP, AGSF

Speaker Disclosures

- T.S. Dharmarajan MD has disclosed that he has no ***relevant*** financial relationship(s) whatsoever, with regards to his presentation

The B Vitamins

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Program Director, Geriatric Medicine Fellowship Program
Montefiore Medical Center (Wakefield Campus), Bronx, NY

Learning Objectives:

By the end of the session, participants will be able to:

- Understand the prevalence and clinical manifestations of vitamin B deficiencies in the long term care setting
- Understand the approach to diagnosis, prevention and management of B vitamin deficiencies
- Be knowledgeable of the food sources of the B vitamins
- Recognize the adverse effects of inappropriate and / or excessive use of micronutrients
- Case presentations and questions to illustrate an understanding of B vitamins

Question 1

1. Which one of the following food items is not a good source of dietary folate?

a. Chicken liver
b. Baker's yeast
c. Milk
d. Chickpeas

Question 2

2. Besides megaloblastosis, which one of the following lab tests suggests vitamin B12 deficiency?

a. Macrocytosis (on blood smear)
b. Blood B12 levels of 325 pg/ml
c. Elevated methymalonic acid levels
d. Elevated homocysteine levels

Question 3

3. You make a diagnosis of malnutrition in a 75 year old adult; one of the deficiencies is a cobalamin level of 100 pg/ml. Which one of the following helps to elucidate the likely cause of B12 deficiency?

a. Anti-parietal cell antibodies in the blood

b. Elevated folate levels and low B12 levels

c. An upper endoscopic examination

d. Dietary habits: consumption of dairy products but no meat, sea food or poultry

Question 4

4. PPIs are commonly used inappropriately on a chronic basis for vague upper gastrointestinal complaints. Which one of the following is an unlikely association of the chronic use of PPIs?

a. Deficiency of vitamin B12

b. Deficiency of folic acid

c. Osteoporotic fractures

d. Iron deficiency

Question 5

5. With regards to treatment of cobalamin deficiency, all the following statements are true, with the exception of:

a. Vitamin B12 deficiency can be prevented by regular use of multivitamin preparations containing B12

b. B12 administered in large oral doses corrects most causes of B12 deficiency including pernicious anemia

c. Correction of B12 deficiency reverses hematological manifestations, but not necessarily neurological deficits

d. B12 must be administered routinely for anticipated deficiency following bariatric surgery

Why Do US Adults Take Vitamins?

- **In long-term care, supplements are commonly prescribed by a health care provider**
- **In clinical practice, reasons to take vitamins include:**
  - **To improve (45%), or maintain (33%) health**
  - **To supplement dietary nutrients**
  - **To maintain bone, joint or heart health**
  - **To lower cholesterol**
- **Multivitamins / minerals are the most commonly used preparations**

Bailey RL et al. Why US adults use dietary supplements. JAMA Intern Med. 2013;173:355-61

Viveky N et al. Use of vitamin and mineral supplements in long term care residents. Appl Physiol Nutr Metab. 2012;37(1): 100-5

Supplement Use in the U.S : Prevalence

- **Vitamin intake is highly prevalent through both prescriptions and over the counter use**
- **Varies with geographic setting, age, gender and other factors**
- **Half the adults in the U.S are on dietary supplements**
- **Prevalence is more in women and older adults**
- **A third use a MVT mineral supplement, with an increase from 30% in 1988-94 to 39% in 2003-2006 NHANES survey years**

Gahche J et al. Dietary supplement use among U.S. adults has increased since NHAMES III (1988-1994). NCHS Data Brief. 2011;61:1-8

The need to screen: A case in point

- **82 yr old community female hospitalized for "crazy behavior". Family unable to care for her at home and wishes to place her in a nursing home**
- **Increasingly forgetful for about 2 years**
- **Confused, agitated, tends to wander**
- **Neurological exam and gait normal**
- **Mini Mental Status examination thrice: scores < 10 out of 30 (limited by language barriers)**

Dharmarajan et al. Vitamin B12 deficiency. Royal Society of Medicine Press. 1999: 9-13

82 year old female: Laboratory tests

- **Hemoglobin, hematocrit, MCV, WBC, platelets normal**
- **Serum iron, TIBC, transferrin saturation: N**
- **Thyroid function normal**
- **Serum folate 14.6 ng/ml (normal)**
- **Serum vitamin B12: 117 pg/ml (200-900)**
- **Methylmalonic acid: 660 nmol/L (high)**
- **Serum homocysteine 16.6 µmol/L (high)**
- **Anti parietal cell and intrinsic factor antibodies positive**
- **CT Scan of the head: Mild diffuse atrophy**

Dharmarajan et al. Vitamin B12 deficiency. Royal Society of Medicine Press. 1999: 9-13

The course

- In the hospital, was disruptive and uncooperative
- Family demanded placement of mom in LTC
- Haloperidol was administered, unimpressive response

- B12 replacement resolved agitation in days
- Behavior improves, patient becomes cooperative

Dharmarajan et al. Vitamin B12 deficiency. Royal Society of Medicine Press. 1999: 9-13

Absorption of Water Soluble vitamins in Health and Disease

- Water soluble vitamins are essential for normal cellular functions, growth and development
- Humans cannot synthesize water soluble vitamins and require them from exogenous sources
- The body depends on normal intestinal absorption of B vitamins
- B12, folate, niacin, pyridoxine, riboflavin and thiamine are absorbed via specific carrier dependent processes
- Interference with any of the following leads to deficiency
  - Defects in absorption
  - Gastro-intestinal disease or resection
  - Drug and alcohol related nutrient interactions
  - Based on the formulation

Said HM. Intestinal absorption of water soluble vitamins in health & disease. Biochem. 2011;437: 357-72

Common disorders in primary care that result from B Vitamin deficiency

Deficiency of B12, folic acid, riboflavin or niacin can lead to:

- **Anemia**
- **Dementia**
- **Neuropathies (including peripheral, spinal, occular)**
- **Neuropsychiatric, including depression**
- **Seizures**
- **Heart failure**
- **Failure to thrive**
- **Glossitis**
- **Skin manifestations (rash, pallor, etc)**

Herbert V et al. Folic acid and B12. Modern Nutrition in health and Disease. 8th ed. 1994; 402-35

Reamy BV et al. Common tongue conditions in primary care. Am Fam Phys. 2010; 81: 627-34

Nutritional Assessment in NH Residents: Be Practical!

- Assess Nutritional Status, through a multidisciplinary approach
  - Weight gain or loss (unintentional?); measure BMI
  - History of gastro-intestinal disease or resection
  - Swallowing difficulty, dementia, depression, refusal to eat
  - Medication review: Drug interactions, adverse effects
- Address abnormal laboratory values
- Altered metabolic needs (sepsis, hyperthyroidism, diabetes)
- Nutrient loses (small intestinal bacterial overgrowth, HF, diuretics, malabsorption)
- Implement a Nutritional Care Plan, avoid restricted diets
- Address possible barriers, environment & supervision

Swagerty D, et al. Nutritional assessment and care of nursing facility residents: A practical approach. JAMDA. 2002; 186-91

Prevalence of B12 Deficiency

Johnson et al (1995)	3 to 44%
Swain et al (1995)	5 to 10% >age 65
Van Goor et al (1995)	3 to 42% > age 65
Stabler et al (1995)	15% >age 65
Carmel et al (1997)	0 to 45%
Dharmarajan et al (97)	25% >age 60

(6% low, 19% marginal)

Prevalence of B12 Deficiency: Dietary Supplement Fact Sheet, 2010

- **Prevalence of deficiency in young adults is greater than previously assumed (Framingham data)**
- **The prevalence is the same in ages 26-49, 50-64, and >65 year groups**

B12 Deficiency and Gender N. Home and Community Older Adults

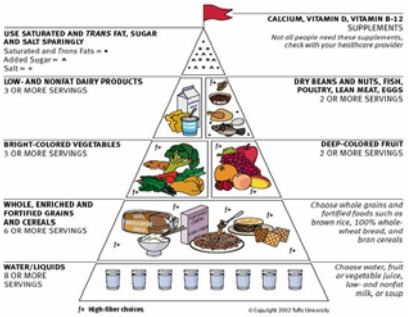
Variable	Female	Male
Age (years)	79.9	78.5
Mean B12 (pg/ml)	675	533
Normal B12 (>350 pg)	77%	71%
Marginal B12 (200-349)	18%	22%
Low B12 (<200 pg)	5%	7%

Dharmarajan et al. Vitamin B12 status in hospitalized elderly from nursing homes and community. JAMDA 2000;1:21-24

Vitamin B12 Requirements

- **Recommended Dietary Allowance (RDA) for Adults over age 14 years: 2.4 µg/day**
- **The preferred form is synthetic rather than as food**

Modified Food Pyramid



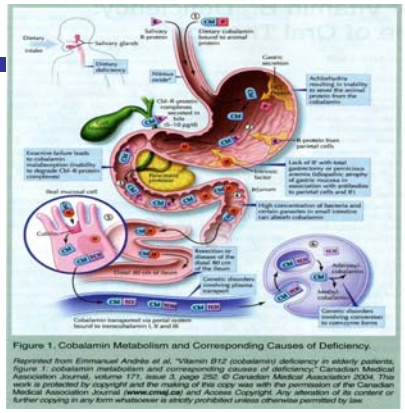


Figure 1. Cobalamin Metabolism and Corresponding Causes of Deficiency.

B12 Absorption: A Complex Pathway

- Dietary B12 is bound to food protein
- Gastric acid and proteolytic enzymes release B12 bound to food in stomach
- 'R' binder protein (haptocorrin) and Intrinsic Factor (glycoprotein) compete for free B12
- B12 preferably binds to R protein from saliva
- Pancreatic enzymes and alkalinity free B12 from R protein in upper small bowel
- Free B12 now attaches to IF (from parietal cells) and moves to lower ileum, attaching to receptors
- B12 transfers to circulating transcobalamin II (TCII)

Herbert V et al. Folic acid and B12. Modern Nutrition in health and Disease. 8th ed. 1994; 402-35

Initial step

Acid Peptic activity separates B12 from food protein and B12 binds to "R" binder

Subsequent step

Alkaline medium & pancreatic enzymes separate B12 from "R" binder and B12 binds to Intrinsic Factor

Vitamin B12: Food Sources

- Average U.S. dietary intake is 5 μg /day
- RDA is 2.4 μg/day, MDR is far less
- Naturally occurring B12 bound to protein, found solely in seafood, organ meats and milk products
- Egg yolk (not the white) contains some B12
- Ultimate source of B12 is microbial synthesis
- For plants to contain B12, they must be contaminated by bacteria (e.g. in legumes)

Herbert V et al. Folic acid and B12. Modern Nutrition in health and Disease. 8th ed. 1994; 402-35

Body Stores of Vitamin B12

- **Average stores : 2 to 5 mg**
- **Range : 1 to 10 mg**
- **Lost via excretion in the bile**
- **Efficient entero-hepatic circulation helps conserve B12**
- **Almost total conservation of B12**
- **Deficiency takes decades to develop (unlike the case of folate)**

Biochemical markers for B12 status

- In mammals, only B12 dependent enzymes are
  - L- methymalonyl - CoA mutase
  - Methionine synthase
- Biochemical markers are metabolites of B12 dependent enzyme activity and may suggest tissue deficiency when elevated
  - Methylmalonic acid (MMA)
  - Homocysteine (Hcys)

Biochemical Reactions Requiring B12

Methylmalonyl CoA synthetase

Methylmalonyl CoA ⟷ Succinyl CoA

Adenosylcobalamin

Methionine synthase

Homocysteine ⟶ Methionine

Methylcobalamin & Methyl Tetrahydrofolate

Homocysteine Levels are Non-Specific: Elevated in Several Disorders

- Cobalamin, folic acid and B6 deficiency
- Hypothyroidism
- Renal failure
- Genetic disorders (↓ cystathione synthase)
- Aging
- Male > female
- Lifestyle (tobacco, coffee, nutrition etc)

Older Adults at Risk for B12 Deficiency

- **Food - cobalamin malabsorption**
- **Atrophic gastritis, including H. pylori infection**
- **Prolonged use of acid lowering agents**
- **Pernicious anemia**
- **Gastric or ileal surgery**
- **Strict vegetarianism**
- **Bacterial overgrowth, blind loops**
- **Crohn's disease**
- **Chronic pancreatitis**
- **Medications: metformin, PPIs etc**

Pernicious Anemia

- A hematological name, but a gastric disease
- Accounts for <10% of causes of B12 deficiency
- Is not a single entity but a collection of disorders
- Anti-parietal cell antibodies present in 90% but are non-specific
- IF antibodies present only in 50%, but specific

Toh BH et al. Pernicious anemia. N Eng J Med. 1997;337: 1441-8

H pylori: a novel causative agent of B12 deficiency

- Initial infection is a mild and superficial gastritis and eventually a chronic gastritis of antrum, body in or both
- *H pylori* appears to be a causative agent of B12 deficiency, from infection over years
- Eradication alone may correct deficiency; B12 levels are restored to normal in < 2 yrs

Kaptan K et al. H. pylori – is it a novel causative agent in vitamin B12 deficiency? Arch Intern Med. 20001; 160: 1349-53

Bacterial Overgrowth Syndrome

- Normally upper GI tract sterile (<10^3 organisms/ml)
- Protective factors: gastric acidity, IgA and motility
- Predisposing factors:
  - Strictures, fistulas, small intestinal diverticulae
  - Diabetes, scleroderma, surgical procedures
- Presentation in the elderly subtle, non-specific
- Malabsorption of nutrients including vitamins; B12 levels low (bacterial utilization), while folate level is high (bacterial production)
- Presence of >10^5 CFU/mL in duodenum diagnostic (breath test)
- Treatment: Correct deficiencies; course of antibiotics

Elphick HL et al. Small bowel bacterial overgrowth. An under recognized cause of malnutrition in older adults. Geriatrics. 2006; 63: 21-6

Vitamin Deficiency in Heart Failure

- Water soluble B vitamins play a key role in energy production
- In a study, a third of ill hospitalized patients had thiamine deficiency
- With HF, 27% had B2 deficiency and 38% had B6 deficiency
- Use of B vitamin supplements alone did not lower deficiency
- Of note: 80% of HF patients were on loop diuretics

Keith ME et al. B vitamin deficiency in hospitalized patients with heart failure. J Am Diet Assoc. 2009; 109: 1406-10

B Vitamins and Cognition in those at Risk for Cardiovascular Disease

- **Women's Antioxidant and Folic acid Cardiovascular Study: 2009 subjects, subjects >65 years**
- **Randomized placebo controlled trial to test a combination of B vitamins (folic acid 2.5 mg, B6 50 mg and B12 1 mg daily) versus placebo for**
  - **Secondary prevention of CVD**
  - **Cognitive function sub study**
- **Combined B vitamins did not delay cognitive decline among women with CVD or CVD risk factors**
- Kang JH et al. A trial of B vitamins and cognitive function among women at high risk of cardiovascular disease. Am J Clin Nutr. 2008; 88 :1602-10

B Vitamins and Cognition

- Taiwanese study, 89 patients with Alzheimer's disease, mean age 75 years
  - Cholinesterase inhibitor and placebo or MVT with B6, B12 and folic acid for 26 weeks
  - No differences in cognition, although homocysteine levels declined

Sun Y et al. Efficacy of MVT supplementation containing vitamins B6, B12 and folic acid as adjunctive tt with a cholinesterase inhibitor in Alzheimer's disease: a 26 week randomized controlled double blind trial in Taiwanese patients. Clin Ther. 2007; 29: 2204-14

Does Lowering the Homocysteine Level Through Use of B vitamins Help?

- Meta-analysis: 11 trials, 22000 participants
- Fact: hyperhomocysteinemia results from B12, folate and pyridoxine deficiency
- But homocysteine lowering through use of B vitamins had no significant effect on cognitive domains, global cognition or cognitive aging
- Nor do the vitamins help in lowering the likelihood of CVD or stroke

Morris MS. The role of B vitamins and cognitive function among women at high risk of CVD. Am J Clin Nutr. 2008;88:1602-10

Clarke R et al Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials, with cognitive data on 22,000 individuals. Am J Clin Nutr. 2012;100:657-66

Deficiency after Roux-en-Y Gastric Bypass

- Prevalence after surgery:
  - Iron deficiency: 40 & 54%, 2 & 3 years post surgery
  - Cobalamin deficiency: 33 & 27%, 2 & 3 yrs post surgery
  - Folic acid deficiency less often observed
- Comment:
  - Routine vitamin supplements inadequate to prevent iron and B12 deficiency
  - Differences in deficiencies noted for different procedures (sleeve gastrectomy vs Roux-en-Y gastric bypass

Vargas-Ruiz AG et al. Obes Surg. 2008; 18: 288-93

Alexandrou A, et al. Cross sectional long term micronutrient deficiencies after sleeve gastrectomy vs Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2014;10:262-9

Do Acid Lowering Agents Affect Vitamin B12 Status in Older Adults?

- PPIs are increasingly used for long periods and often in absence of clear cut indications
- H2 blockers and PPIs diminish gastric acid production
- Hypochlorhydria may interfere with release of B12 from food protein
- Lack of acid encourages bacterial overgrowth in small intestine, which competes for B12

Dharmarajan TS, et al. Do acid lowering agents affect vitamin B12 status in older adults? J Am Med Dir Assn. 2008; 9: 162-7

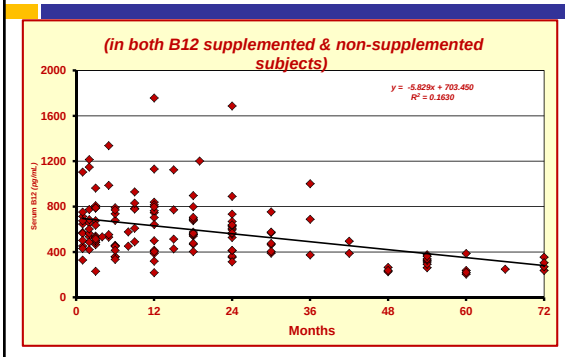
Acid Lowering Agents and B12

- Study of 542 community and NH adults, 60-102 yrs, 63% Female
- 54% were on ALA: 26% on PPIs, 28% H2Blockers (H2B)
- Duration: 1 to 72 months (avr. 18.2)
- H2B use did not influence B12 status
- PPI use was associated with diminished levels
- Concomitant oral B12 supplements did not prevent the decline in B12 status
- Deficiency take years to develop
- In these patients, crystalline oral B12 (non food-bound B12) is likely to be absorbed
- Periodic B12 screening is appropriate in those on PPIs

Dharmarajan TS, et al. Do acid lowering agents affect vitamin B12 status in older adults? J Am Med Dir Assn. 2008; 9: 162-7

Serum B12 levels vs. Months of PPI Use

Dharmarajan TS, et al. Do acid lowering agents affect vitamin B12 status in older adults? J Am Med Dir Assn. 2008; 9: 162-7



Metformin Related B12 Deficiency

- B12-IF complex uptake by ileal cell membrane receptors is calcium dependent
- Metformin affects Ca dependent membrane action
- This is reversible by administering oral calcium
- Value of screening for B12 status if on metformin?

- Note: Diabetics may also have slow intestinal transit with resultant bacterial overgrowth and malabsorption

Kin Wah Liu et al. Age and Aging. 2006; 35: 200-1

B12 Deficiency: Manifestations

- **Asymptomatic**
- **Hematological**
- **Psychiatric**
- **Neurological**
- **Any combination of above**

- **Stages of Vitamin B12 deficiency**

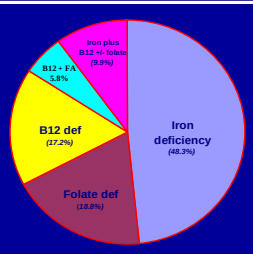
B12 Deficiency: Presentations

The diagnosis can be easily missed, because:

- Many are totally asymptomatic
- May present with everyday symptoms, such as fatigue, lethargy, tiredness, absent-mindedness or depression
- May coexist with other diseases e.g. Alzheimer's
- Rapid onset, rare, with nitrous oxide anesthesia
- Classic hematological or neurological disorder

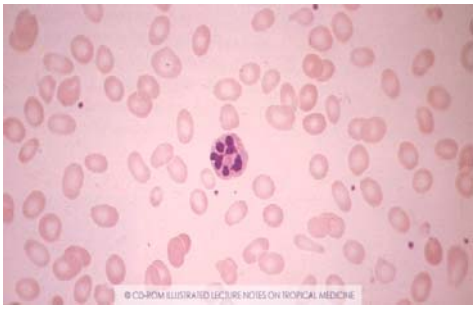
Dharmarajan TS et al. Vitamin B12 deficiency: recognizing subtle symptoms in older adults. Geriatrics. 2003;58:30-8

Nutritional Anemias* (NHANES III, 1988-1994)



* WHO criteria for Anemia: Men: Hb <13 g/dL, Women < 12 g/dL

Vitamin B12 Deficiency: Peripheral smear



Diagnosis of B12 Deficiency

- Blood: CBC, MCV, peripheral smear
- Serum B12 levels
- Serum Methylmalonic acid
- Serum Homocysteine
- Serum Holotranscobalamin
- Bone marrow evaluation
- Specific tests to elucidate cause of deficiency
  - IF assay, Schilling test, H. pylori testing, etc

False normal and false low levels

- **Falsely normal**
  - True deficiency
  - Myeloproliferative disorders
  - Liver disease
  - Congenital TCII deficiency
  - Intestinal bacterial overgrowth
- **Falsely low**
  - Folate deficiency
  - Oral contraceptives, pregnancy
  - Congenital haptocorin deficiency
  - Multiple myeloma
  - Excess vitamin C intake

Is Screening justified for B12 status? Viewpoints Differ!

- Common, under-recognized, myriad of presentations
- "Prevention better than cure" an applicable fact with B12
- Disability (when untreated) can be devastating
- Consider a screening approach
- Administer B12 to all elderly regardless of levels
- Traditional approach: individualized evaluation, therapy
- Treatment is inexpensive and virtually free of side effects

Carmel R. How I treat cobalamin (B12) deficiency. Blood. 2008; 112: 2214-21

Stabler SP. Screening the older population for cobalamin (B12) deficiency. J Am Geriatr Soc. 1995;43: 1290-98

Dharmarajan TS et al. An algorithmic approach to screening for vitamin B12 status and treatment of identified deficiency. In Herbert V ed. Vitamin B12 deficiency. Royal Society of Medicine Press. 1999; 49-51

Carmel R. Cobalamin, the stomach and aging. Am J Clin Nutr. 1997;66: 750-9

Suggested Approach to B12 status

- **Screen individuals at risk at first opportunity, irrespective of the age**
- Initiate consider screen at 65, periodically when indicated
- Levels <100 are likely to be deficiency
- Levels > 350 pg/ml, deficiency unlikely
- Levels between100-350 pg/ml are indeterminate (not uncommon); may consider further tests
  - MMA, homocysteine, holotranscobalamin to confirm status
- Specific tests to the etiology are best individualized

Carmel R. How I treat cobalamin (B12) deficiency. Blood. 2008; 112: 2214-21

Stabler SP. Screening the older population for cobalamin (B12) deficiency. J Am Geriatr Soc. 1995;43: 1290-98

Dharmarajan TS et al. An algorithmic approach to screening for vitamin B12 status and treatment of identified deficiency. In Herbert V ed. Vitamin B12 deficiency. Royal Society of Medicine Press. 1999; 49-51

Principles of Management

- Consider treatment when B12 levels are clearly low or if marginal, with ↑ MMA and/or Hcys
- With deficiency and no symptoms, oral or injection B12 may be used to replenish stores
- With deficiency + complications (neurological), initiate by injection therapy to rapidly correct status
- Maintenance with oral B12 must be with large doses
- No B12 toxicity reported with high doses
- While on injection therapy, do not measure levels
- With oral therapy, periodically measure levels
- Treatment is usually for life
- Individualize approach to patient preferences and cost

Carmel R. How I treat cobalamin (B12) deficiency. Blood. 2008; 112: 2214-21

Stabler SP. Screening the older population for cobalamin (B12) deficiency. J Am Geriatr Soc. 1995;43: 1290-98

Dharmarajan TS et al. An algorithmic approach to screening for vitamin B12 status and treatment of identified deficiency. In Herbert V, ed. Vitamin B12 deficiency. Royal Society of Medicine Press. 1999; 49-51

Treatment of B12 Deficiency

- **Intramuscular**
  - Commonly used, safe, reliable, inexpensive
  - Initiation and maintenance: 100-1000 mcg, Q 1-3 months
- Intranasal
  - Weekly instillation of intranasal gel 500 μg
- **Oral**
  - Useful in strict vegans, with or without IF
  - Large doses effective even in pernicious anemia (no IF)
  - Least reliable, compliance influences results
- **Sublingual**
  - Effective, convenient alternative form of administration
  - Dose: Cobalamin nuggets 2000 μg daily

Delpre et al. Lancet, 1999;354:740-1

Andres E et al. Efficacy of oral cobalamin (vitamin B12) therapy. Expert Opin Pharmacother 2010. 11: 249-56

Carmel R. How I treat cobalamin (B12) deficiency. Blood. 2008; 112: 2214-21

Does Oral B12 correct deficiency?

- Was widely believed that patients with PA cannot absorb adequate B12; this is contradicted by several studies
- In Sweden, oral B12 is in use for 30 years, in 40% of pts
- Works through transport system that is not dependent on IF or the terminal ileum
- About 1% of large doses (300-100,000 μg) absorbed by this route
- In a study, oral cyanocobalamin administered in doses of 250-1000 mcg/d for 1 month
  - Blood levels increased similarly in both food-cobalamin and pernicious anemia groups
  - Macrocytosis was corrected in 100%, anemia in 54%

Troilo A et al. Presse Med 2010. 39: e273-9

Andres E et al. Efficacy of oral cobalamin (vitamin B12) therapy. Expert Opin Pharmacother 2010. 11: 249-56

B12: Dietary Supplement Fact Sheet, 2010

- Synthetic B12 added to fortified foods and supplements is in free form, usually cyanocobalamin
- Approx. 56% of a 1 mcg oral dose is absorbed
- About 10 mcg of a 500 mcg oral dose is absorbed
- Prevalence of deficiency is common in young and old
- Fortified cereals: is one of the few sources for vegans
- B12 supplements do not help in absence of deficiency
  - B12 is not toxic in large amounts (up to 25000 μg)
  - B12 therapy in deficiency states may lead to a drop in potassium and phosphorus levels, with related morbidity

Folic Acid

- Terms: Folic acid or folate?
  - Folic acid stable in solution, the form in supplements, 100% bioavailability
  - Folate in food, blood, tissues is oxidized easily
  - Reduced folate in food availability is <50%; over half lost in frying or boiling
  - Red cell or serum folate: RBC folate is stable and fluctuates little over time
- Folate is present in virtually all foods
  - Dairy, poultry, meat (liver, kidney), seafood, fruits, vegetables, nuts
  - Highest concentration: yeast, spinach, liver, peanuts, kidney beans
  - Fortification of cereals and grains is mandated in the U.S.: 140 μg/100g
- Absorption of folate occurs in the jejunum
- RDA: 400 μg /d

Carmel R. Folic Acid. Modern Nutrition in Health and Disease. 2006; 470-81

Folate Deficiency in the NH

- Risk factors are common in the NH and prevalence is high
- Nutritional Status
  - Swallowing disorders
  - Dementia, depression, refusal to eat
  - Restricted diets
  - Small intestinal bacterial overgrowth
  - Malabsorption from any cause
- Medication review and toxins
  - Methotrexate, sulfa trimethoprim, alcohol, sulfasalazine, hydantoins etc
- Altered metabolic needs (hyperthyroidism)
- Nutrient loses (exfoliative dermatitis, HF)

Smith RL. Evaluation of vitamin B12 and folate status in the nursing home. JAMDA. 2001; 230-8

Folate Deficiency : Treatment

- Cheap and effective to give folic acid supplements
- Folic acid over the counter dosed generally <400 μg
- Higher doses (1 mg) available by prescription (rarely up to 5 mg)
- Injections are effective
- Rule out cobalamin deficiency before administration of folic acid
  - A serious potential error is to provide folic acid to someone with unrecognized B12 deficiency
  - Administered folic acid bypasses the methyl-THF trap of B12 metabolism and reverses anemia; but B12 deficiency progresses with possible irreversible and accelerated neurological deterioration

Carmel R. Folic Acid. Modern Nutrition in Health and Disease. 2006; 470-81

A Comparison of B12 and Folic Acid

Variables	B12	Folic Acid
Presentation	Asymptomatic, hematologic, dementia, depression, psychiatric	Asymptomatic, hematologic, depression, cognitive
Causes	Vegan, several GI causes, medications	Restricted diet, alcoholism, excess utilization or loss
Diagnosis	Megaloblastosis B12 levels MMA, tHcy , holoTC	Megaloblastosis Folate levels tHcy assay
Treatment	Oral, IM, S/L, I/nasal	Oral, IM
Diet	Animal sources	Vegetables, fruits and animal sources
Fortification	Not implemented	A public health initiative

Sources of B12 and Folic Acid

Content	B12	Folic Acid
High	Mollusks, clams, crab	Bakers yeast, turkey
High	Beef, liver, turkey	Chicken liver, beef
High	Chicken, pork, sausage	Whole grain rice
Moderate	Milk, buttermilk	Spinach, lentils
Moderate	Egg yolk, cheese	Chickpeas, peanuts
Moderate	Mozzarella, dry milk	Okra, lettuce, beans
Low to absent	Vegetables, fruits	Oil, margarine, cream
Low to absent	Nuts, peas, beans	Milk, fish, mollusks
Low to absent	Grains, oils, butter	Apple/cranberry juice

Macrocytosis and Differential Diagnosis

- Normal MCV is 83-97 fl
  - Most macrocytic anemias are non-megaloblastic, & not due to B12 or folate def
  - Microcytosis from iron deficiency can blunt macrocytosis
- Causes of macrocytosis
  - Reticulocytosis (any cause; e.g. hemorrhage, hemolysis)
  - Vitamin B12 and folate deficiency
  - Myelodysplasia
  - Chronic liver disease
  - Chronic alcoholism
  - Hypothyroidism
  - Chemotherapeutic or immunosuppressive agents
  - Artifactual (severe hyperglycemia / cold agglutinins with RBC clumping)

Carmel R. Folic Acid. Modern Nutrition in Health and Disease. 2006; 470-81
Smith RL. Evaluation of vitamin B12 and folate status in the nursing home. JAMDA. 2001; 230-8

Thiamin (Vitamin B1)

- Thiamin is a critical risk factor in glycolysis and oxidative decarboxylation of carbohydrates for energy production
- Deficiency : unrecognized and under-diagnosed
  - Thiamin deficiency is common and associated with increase in mortality
  - Symptoms are nonspecific in the critically ill patients
  - Wet beriberi involves the heart: high output failure with tachycardia
  - Dry beriberi mainly neurological with symmetrical sensory and motor involvement
  - Wernicke Encephalopathy: ocular palsies, nystagmus, ataxia, disordered mentation
  - Korsakaoff: amnestic-confabulatory syndrome with antero and retro grade amnesia
  - Scenarios: burns. alcoholism, starvation, unexplained HF, malnutrition
- Failure to suspect deficiency can lead to permanent cognitive and physical disabilities requiring life long care

Donnino MW et al. Thiamine deficiency in critically ill patients with sepsis. J Crit Care. 2010; 25: 576-81
Manzanares W et al. Thiamine supplementation in critically ill. Curr Opin Clin Nutr Metab Care. 2011. 14: 610-7

Thiamin (Vitamin B1)

- Thiamin turnover is high in the brain
- Prolonged glucose supplementation without thiamine is a risk factor for Wernicke encephalopathy
- Brain MRI can demonstrate classic thalamic injury
- Sources
  - Highest in yeast and germ of cereals
  - Most cereals and breads now fortified
  - Milk, sea food, fruits poor sources.
  - Much loss from discarding cooking water
- Response to thiamin 50-100 mg IV or IM is rapid both for wet beriberi and Wernicke encephalopathy

Butterworth RF. Thiamin. Modern Nutrition in Health and Disease. 2006; 426-33
Manzanares W et al. Thiamine supplementation in critically ill. Curr Opin Clin Nutr Metab Care. 2011. 14: 610-7

Riboflavin (B2)

- Riboflavin fluoresces yellow-orange to give a yellow-white hue to egg white and milk
- Thiamine exists in 2 coenzyme forms (FMN and FAD)
  - Contributes to cellular growth, enzyme function and energy production
  - Cofactor in carbohydrate, fat and amino acid metabolism
  - Improves iron absorption
  - Alcohol decreases its absorption and reduces bioavailability
  - May play a role in homocysteine homeostasis
- Nutrient interactions: nutrients depend on riboflavin for homeostasis
  - Deficiency may result in additional deficiencies of folate, B6 and B12

Riboflavin: Alternative Medicine Review. 2008; 13 (4): 334-9
McMorick DB. Riboflavin. Modern Nutrition in Health and Disease. 2006; 434-41

Riboflavin (B2) Deficiency

- Deficiency causes
  - Angular stomatitis, glossitis, seborrhea, neuropathy
  - Anemia, that is normochromic, normocytic
  - Cataract, data is conflicting
  - Role in migraine prophylaxis?
- Sources
  - Milk, eggs, meat, yogurt, cheese, almonds, green vegetables
  - Improper storage of milk, eggs, vegetables results in loss from food
- Dose
  - Daily dose ranges considerably, typically 10-50 mg daily
  - No toxicity reported with large doses

Riboflavin: Alternative Medicine Review. 2008; 13 (4): 334-9

Nicotinic Acid (Niacin)

- Used for decades to prevent and treat atherosclerosis
  - Has antidyslipidemic effects, which are complex
  - Nicotinic acid receptor in adipocytes and immune cells may play role
  - Precursor to NAD / NADP; oxidation-reduction and other reactions
- Niacin and nicotinamide are absorbed by diffusion
- Deficiency characterized by:
  - Pellagra: pigmented rash, diarrhea, memory loss, depression
  - D's: diarrhea, dermatitis, dementia, delirium
- Blood assay of NAD/NADP (nicotinamide adenine dinucleotide and phosphate) helps make diagnosis of deficiency

Lukasova M et al. Nicotinic acid (niacin): new lipid-independent mechanisms of action and therapeutic potentials. Trends Pharmacol Sci. 2011; 32: 700-7
Hartman R et al. Acanthosis nigricans in the setting of niacin therapy. Dermatol Online. 2011; 17: 11

Nicotinic Acid (Niacin)

- Sources
  - Meat, fish and nuts are good sources
  - Milk and eggs contain small amounts
- Requirements in niacin equivalents (conversion of trytophan to niacin); 1 mg niacin = 60 mg tryptophan; RDA is 14-60 mg
- Decreases LDL cholesterol and triglycerides; increases HDLC
- Niacin, the Pharmacological agent: several formulations
  - Immediate release up to 3 g/d (high flushes)
  - Sustained release 1.5-2 g/d (less flushes)
  - Extended release: effective like immediate, reduced flushes
  - Topical application available, intent to circumvent side effects
- Side effects
  - Flushes; reversible acanthosis nigricans; glucose intolerance; liver toxicity

Burgeois C et al. Niacin. Modern Nutrition in Health and Disease. 2006; 442-51

Vitamin B6 (Pyridoxine)

- B 6 is a generic term for pyridoxine, pridoxamine and pyridoxal (there are 6 active vitamers of B6)
- Action: cofactor in over 140 enzyme reactions involving lipids, carbohydrates, glycogen and immune function
- Interactions with zinc, folate, niacin, riboflavin and medications
- Deficiency : refractory seizures, esp. in the critically ill
- RDA: 1.3 mg/d
- Sources in food are widespread
  - meat, fish, eggs, dairy, vegetables, grains, chicken and fortified cereals

Disalvo ML. et al. Vitamin B6 salvage enzymes: mechanism, structure and regulation. Biochem Biophys Acta. 2011;1824: 1597-608

Gerlach At et al. Vitamin B6 deficiency: a potential cause of refractory seizures in adults. JPEN 2011; 35: 272-5

Terminology: Dietary Reference Intake (DRIs)

- **Recommended Dietary Allowance (RDA)**
  - **Average daily nutrient intake sufficient to meet requirements of 97-98% of healthy individuals**
- **Estimated Average Requirements (EAR)**
  - **Average daily nutrient intake estimated to meet the requirements of half the healthy individuals in a particular life stage and group**
- **Tolerable Upper Level Intake (UL)**
  - **Is the highest average daily nutrient intake that poses no adverse health effects to almost all individuals**

Thank You!

VITAMINS OR NO VITAMINS?

VITAMINS D AND K

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VITAMINS D AND K

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Speaker Disclosures

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- Dr. N. Pandya has disclosed that she has no relevant financial relationship(s) with regards to her presentation

OBJECTIVES

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By the end of the session, participants will be able to:

- Understand the physiologic role and clinical manifestations of vitamin D and K deficiencies in the long term care setting
- Understand the approach to diagnosis, prevention and management of vitamin D and K deficiencies
- Be knowledgeable of the food sources of these vitamins
- Recognize the adverse effects of inappropriate and / or excessive use of micronutrients

Vitamin D

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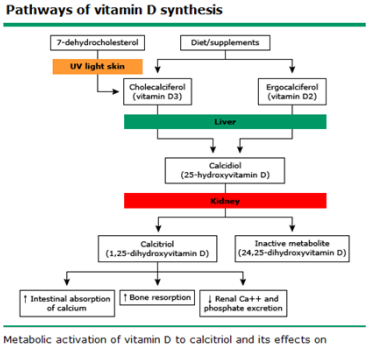
- Vitamin D is a fat-soluble vitamin
- Very few foods naturally contain vitamin D (fatty fish livers are the exception)
- Dermal synthesis is the major natural source of the vitamin
- Vitamin D from the diet or dermal synthesis is biologically inactive and requires enzymatic conversion to active metabolites



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Physiologic role of Vitamin D

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- Calcium homeostasis and bone metabolism.
- 25-hydroxyvitamin D (25[OH]D) is the major circulating form of vitamin D
- Half-life of two to three weeks, compared with 24 h for parent vitamin D
- In the renal tubule, entry of the filtered 25(OH)D-vitamin D-binding protein complex into the cells is facilitated by receptor-mediated endocytosis
- Two proteins cubilin and megalin are receptors that facilitate uptake in proximal tubule
- Deficiency of either protein results in increased urinary excretion of 25(OH)D in the urine

Noncalcemic Functions of $1,25(OH)_2D$

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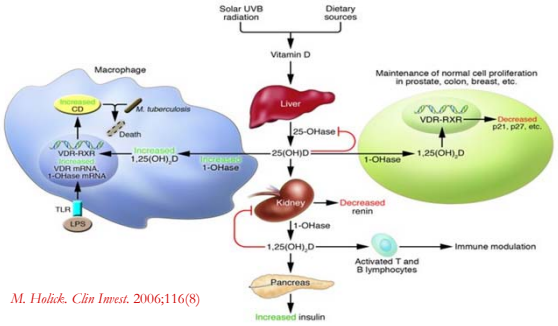

M. Holick. Clin Invest. 2006;116(8)

Noncalcemic Functions of $1,25(OH)_2D$

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- Can stimulate the pancreas to produce insulin
- Downregulates the renal production of renin
- Interacts with its nuclear receptor (VDR) in a wide variety of tissues and cells; helps maintain normal cell proliferation and differentiation
- 25(OH)D can also be converted to 1,25(OH)2D invariety of cells, including colon, prostate, and breast, for the autocrine production of 1,25(OH)2D
- important for regulating cell growth; decreases risk of the cell becoming malignant

M. Holick. Clin Invest. 2006;116(8)

Noncalcemic Functions of $1,25(OH)_2D$

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- 25(OH)D also is metabolized in macrophages by the 1-OHase to produce 1,25(OH)2D
- The expression of the VDR and 1-OHase is upregulated when TLR2/1 is stimulated by LPS
- The increase production of 1,25(OH)2D increases the nuclear expression of cathelicidin (CD) in the macrophage- a cationic peptide that causes the destruction of infective agents including *M. tuberculosis*
  - *Cod liver oil and heliotherapy*

M. Holick. Clin Invest. 2006;116(8)

CASE: A 76 yr. old retired nurse with severe weakness

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- Admitted for rehabilitation following an episode of right lower lobe pneumonia and severe weakness
- PMH: HTN, bariatric surgery for obesity at age 60, subclinical hyperthyroidism, right mastectomy at age 42, and anemia
- Medications: amlodipine 5mg/d, moxifloxacin 400 mg/d, MVI, fish oil TID, ferrous sulfate 325 mg/d, prilosec 20 mg/d, B12 1000 mcg/d11

Case: poor progress with PT and OT; fell while going to the bathroom

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- Exam: 158/90, HR 86 reg, afebrile, RR 20
- Alert, witty but apathetic.
- "I'm just washed out"
- Pale conjunctivae, depressed affect, partial thyroidectomy scar
- Normal hear sounds, few right basal ronchi, R mastectomy scar without local recurrence, normal L breast exam, non-tender abdomen with midline scar
- Unable to stand unassisted from chair, painful upper arms and thighs, waddling gait

Case: Laboratory Tests

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- Hb 10.9 g/dL (12-15)
- WBC 12.0 x10^9/L
- MCV 95 fL (80-100)
- Electrolytes, BUN, Cr normal
- TSH 1.1 mIU/L (0.5-5)
- Free T4 0.95 ng/dL (0.8-1.8)
- 25 OH Vit D 9 ng/ml (5-75)

Vitamin D deficiency- definition

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- A 25(OH)D blood level of 30 ng/ml (75 nmol/L)
- Subclinical vitamin D deficiency, as measured by low serum 25(OH)D, is very common
- In the National Health and Nutrition Examination Survey (NHANES) 2005 to 2006, 41.6 percent of adult participants (≥20 years) had 25(OH)D levels below 20 ng/mL (50 nmol/L)
- The total diet and supplement intakes for adult American males over 50 years was 380 IU, and for females, 402 IU

Regan L. Bailey RL et al. Estimation of Total Usual Calcium and Vitamin D Intakes in the United States J. Nutr. 2010: 140: 817–822, 2010.

Clinical manifestations of Vitamin D deficiency

Holick. Nutrients 2013.5(1)

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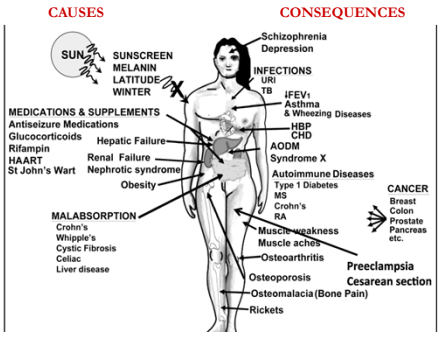

DEFICIENCY AND RESISTANCE- Four general causes

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- Impaired availability of vit D
  - inadequate dietary vit D
  - fat malabsorptive disorders
  - and/or lack of sunlight (photoisomerization)
- Impaired hydroxylation by the liver to produce 25[OH]D
- Impaired hydroxylation by the kidneys to produce 1,25-dihydroxyvitamin D (CKD)
- End organ insensitivity to vitamin D metabolites (hereditary vitamin D-resistant rickets)

Other factors contributing to vit D deficiency

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- Age (stores decline), especially in winter;
  - even in healthy adults- 36% of 69 subjects, 18 to 29y had vitamin D levels <20 ng/mL in winter
- Glucocorticoids used chronically in high doses (inhibit calcium absorption)
- Hospitalized status (57% deficient in a general medical service)
- Women treated for osteoporosis have unrecognized vit D deficiency
- Gastric bypass (especially long-limb compared to short limb)
- Immigrants to cold climates from warm climates Asian Americans)
- Advanced cystic fibrosis
- Extensive burns
- Nephrotic syndrome (excretion of vit D binding protein and 25(OH)D

Tangpricha V, et al. Am J Med. 2002;112(8):659.

Thomas MK et al. N Engl J Med. 1998;338(12):777

Drugs and vitamin D deficiency

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- Decreased circulating levels of calcidiol 25(OH)D, may also occur in patients treated with
  - phenytoin,
  - phenobarbital,
  - carbamazepine,
  - isoniazid,
  - theophylline, and rifampin

Increased catabolism of calcidiol

Supplementation may be necessary (400 to 4000U/d)

Collins N et al. Q J Med. 1991;78(286):113.

Dietary Sources of Vitamin D

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Source	Vitamin D content
Fortified milk	100 IU/8 oz
Fortified orange juice	100 IU/8 oz
Infant formulas	100 IU/8 oz
Fortified yogurts	100 IU/8 oz
Fortified butter	56 IU/3.5 oz
Fortified margarine	429 IU/3.5 oz
Fortified cheeses	100 IU/3 oz
Fortified breakfast cereals	~100 IU/serving
Egg yolk	~20 IU/yolk
Shiitake mushrooms, fresh	100 IU/3.5 oz
Tuna, canned	236 IU/3.5 oz
Mackerel, canned	~250 IU/3.5 oz
Sardines, canned	~300 IU/3.5 oz
Salmon, canned	~300–600 IU/3.5 oz
Salmon, fresh	~400–500 IU/3.5 oz
Shiitake mushrooms, sun-dried	1,600 IU/3.5 oz
Drisdol (vitamin D_2) liquid	8,000 IU/cc
Cod liver oil	400 IU/tsp

Prevalence of Vitamin D Deficiency in Nursing Homes

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- In a Veterans facility, (N=229)
  - 51% had vitamin D deficiency (25[OH]D <30 ng/mL)
- In a Spanish nursing home
  - 87% of patients had low vitamin D; 21.8% of them had secondary hyperparathyroidism
- In a Japanese nursing home study (N=133)
  - 60% had low vitamin D, and 16% had secondary hyperparathyroidism

- Braddy KK et al. ***J Am Med Dir Assoc.*** 2009; 10: 653–657
- Larrosa M. et ***Medicina Clinica*** 2001 117:16
- Nashimoto M et al. **Aging - Clinical and Experimental Research** 2002 **14:1 (5-12)**

Adverse Musculoskeletal Outcomes Associated with Low Vitamin D Serum

21

- Serum concentrations <30 ng/mL (<75 nmol/L) have been associated with
  - balance problems
  - impaired lower extremity function
  - higher fall rates
  - lower bone mineral density
  - muscle weakness

- Bischoff-Ferrari HA et al. Am J Clin Nutr 2004a;80:752-8
- Flicker L,et al.. J Am Geriatr Soc 2005;53:1881-8.

Relationship between vitamin D levels and BMD, gait speed, alveolar attachment, and fractures.*

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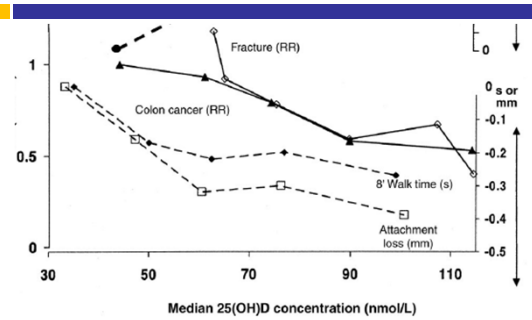
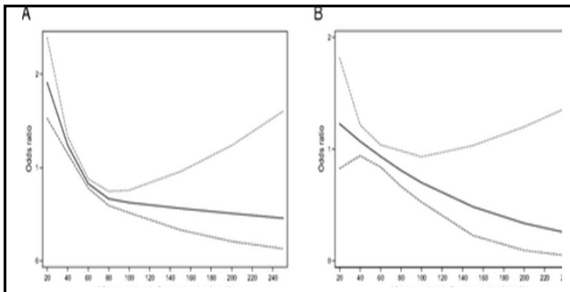


Bischoff-Ferrari HA et al. Am J Clin Nutr 2006a;84:18-28.



Odds ratio of Prevalent and Incidental Frailty with changing vitamin D levels

- Prospective cohort study; 4023 men aged 70-88 y in W. Australia
- OR of FRAILTY increased 1.96 in the lowest quartile compared to the highest

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Yuen YE et al. JCENM June 2013

Association of Vitamin D and Cardiovascular Risk

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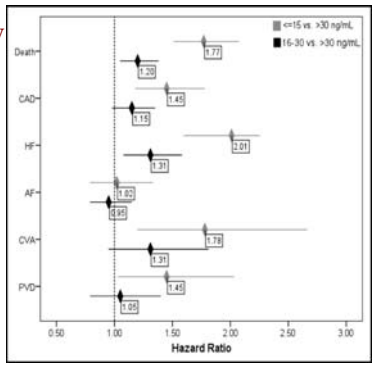
- Significant inverse association between 25(OH)D serum levels and cardiovascular risk
- Vitamin D receptor is present in endothelium, vascular smooth muscle, and cardiomyocytes
- May protect against atherosclerosis through the inhibition of macrophage cholesterol uptake, reduced vascular smooth muscle cell proliferation
- Increased insulin resistance and pancreatic β-cell dysfunction, predisposing to the metabolic syndrome and DM
- Obesity is associated with a lower vitamin D status due to a sequestration and volumetric dilution of the lipophilic vitamin D

Reid, I.R.; Bolland, M.J. *Heart* **2012,**

Intermountain Collaborative Study

N=41, 504
Av age 55 ± 21y

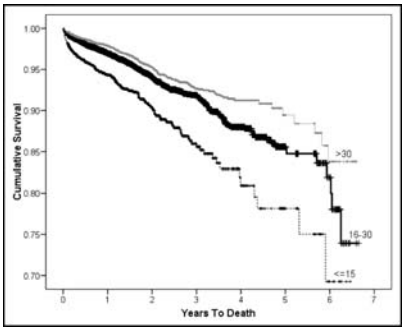
Vitamin D deficiency was associated with highly significant (p <0.0001) increases in the prevalence of diabetes, hypertension, hyperlipidemia, and peripheral vascular disease.



American Journal of Cardiology 2010 106, 963-968

Intermountain Collaborative Study

Survival differed significantly by initial vitamin D level



American Journal of Cardiology **2010 106, 963-968**

Vitamin D deficiency in elderly people is associated with increased mortality

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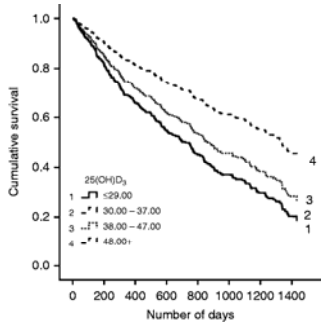
- The Study of Health and Drugs in the Elderly (SHADES); prospective cohort study among elderly people (>65 years) in 11 nursing homes in Sweden
- N=333; follow-up period 3 yr
- Compared with the subjects in Q4 (25(OH)D_3 >48 nmol/l), HR for mortality was 2.02 in Q1 (25(OH)D_3 <29 nmol/l) (P<0.05)
- 80% had 25(OH)D_3 below 50 nmol/l

Samefors M et al. Eur J Endocrinol 2014;170:667-675

Figure 2 Cumulative survival according to 25(OH)D3 quartiles.



Samefors M et al. Eur J Endocrinol 2014;170:667-675

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American Geriatrics Society Consensus Statement on Vitamin D for Prevention of Falls and Their Consequences

American Geriatrics Society Workgroup on Vitamin D Supplementation for Older Adults 2013

Selected Recommendations

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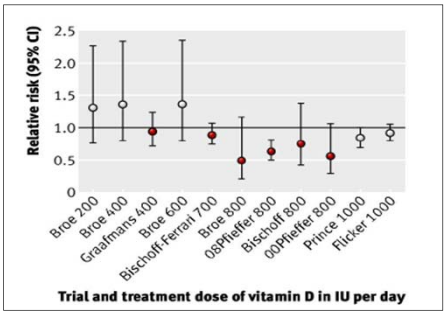
- **STATEMENT 1b**: There are insufficient data at this time to support a recommendation for increased vitamin D supplementation without calcium for older persons residing in the community or in institutional settings
- **STATEMENT 2**: Clinicians are strongly advised to recommend vitamin D supplementation of at least 1,000 IU/d with calcium to older adults residing in institutionalized settings to reduce the risk of fracture and falls

American Geriatrics Society Workgroup on Vitamin D Supplementation for Older Adults 2013



Meta-analysis of 11 trials of oral vitamin D supplementation (Bischoff-Ferrari, 2011)

Higher dosages were associated with a reduction in nonvertebral fractures of 29%
Fractures in institutionalized older individuals decreased by 15%.

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Selected Recommendations

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- **STATEMENT 3**: Clinicians should review older adults' vitamin D intake from all sources (diet, supplements, sunlight) and discuss strategies to achieve a total vitamin D input associated with fall and fracture prevention
  - Recommend an average daily input from all sources of 4,000 IU for all older adults
  - Should result in approximately 92% of older adults in the US achieving target 25(OH)D (>30 ng/ml) levels regardless of skin pigmentation, obesity, or sun exposure

American Geriatrics Society Workgroup on Vitamin D Supplementation for Older Adults 2013

Selected Recommendations

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- **STATEMENT 4a**: Routine laboratory testing for 25(OH)D serum concentrations before supplementation begins is not necessary.
- **STATEMENT 4b**: It is not necessary for clinicians to routinely monitor 25(OH)D for safety or efficacy when supplementation is within the recommended limits
- **STATEMENT 4c:** If clinicians choose to monitor 25(OH)D, they are advised to test after 4 months of vitamin D3 supplementation to confirm that appropriate levels have been achieved

American Geriatrics Society Workgroup on Vitamin D Supplementation for Older Adults 2013

Monitoring should be considered in the following settings

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- Patients taking medications which either bind vitamin D in the gut or accelerate the breakdown of vitamin D (e.g. cholestyramine; inducers of the cytochrome P450 pathway
- Obesity: BMI >30 kg/m2 or body mass >90 kg
- Malabsorption syndromes
- Patients who limit their vitamin D intake from all sources below recommended intake

Blum M, Dallal GE, Dawson-Hughes B. J. Am. Coll. Nutr., April 1, 2008; 27(2): 274 - 279.

Selected Recommendations

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- **STATEMENT 5:** Because of the different pharmacokinetic profiles of vitamin D2 and vitamin D3, clinicians should recommend vitamin D3 supplementation intervals of 4 months or less and vitamin D2 supplementation intervals of 14 days or less
  - large bolus doses of vitamin D2 or D3 (≥300,000 IU) should not be recommended
  - longer intervals between doses of vitamin D2 will result in large fluctuations of serum 25(OH)D
  - Calciferol = vitamin D2; Cholecalciferol = vitamin D3

American Geriatrics Society Workgroup on Vitamin D Supplementation for Older Adults 2013

Vitamin D supplementation

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- Vitamin D3 is available as nonprescription, over-the-counter products in dosages of 400, 800, 1,000, 2,000, 5,000, and 10,000 IU.
- A 50,000-IU formulation of D3 is currently available online
- Vitamin D2 is available in a prescription form of 50,000 IU (more expensive but readily available at pharmacies)
- Use of the prescription product at 50,000 IU vitamin D2 per dose to influence serum 25(OH)D levels is an *off-label* use of the drug

American Geriatrics Society Workgroup on Vitamin D Supplementation for Older Adults 2013

Vitamin D Intoxication

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- Excessive biologic action of the vitamin, possibly consequence of increased levels of 25(OH)D of the active metabolite $1,25(OH)_2D$
- Hypercalcemia
- Hypercalciuria
- Polydipsia, polyuria
- Confusion
- Anorexia, vomiting
- Chronic intoxication may cause;
  - nephrocalcinosis,
  - bone demineralization and pain

Morgan SL, Weinsier RL. Fundamentals of clinical nutrition, Mosby, St. Louis 1998.

Adverse Effects of Excess Vitamin D

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- Documented in adults taking > 40,000-100,000 IU/d
- Excessive exposure to sunlight does not lead to vitamin D poisoning, limited capacity to form 7-dehydrocholesterol
- Diagnosis by documenting elevated levels of 25(OH)D >100 mg/mL
- **Treatment**
  - Restriction of dietary calcium intake
  - Hydration
  - Vitamin D stores in fat may be substantial, and intoxication may persist for weeks
  - Such patients are responsive to glucocorticoids (100 mg/d of hydrocortisone)

39 VITAMIN K

Forms of Vitamin K

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- A fat-soluble vitamin
- Two natural forms of vitamin K:
- Vitamin K1, also known as *phylloquinone*, from vegetable and animal sources
- Vitamin K2, or *menaquinone*, which is synthesized by bacterial flora and found in hepatic tissue
- Phylloquinone can be converted to menaquinone in some organs.

Actions of Vitamin K

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- Cofactor required for the activity of several key proteins containing carboxyglutamic acid residues
- **Coagulation pathway**: essential for activity of several carboxylase enzymes within the hepatic cells; therefore necessary for the activation of coagulation factors VII, IX, X, and prothrombin
- **Antithrombotic effects of proteins C and S** :The natural anticoagulants, proteins S and C also require vitamin K for their activity

Davie EW SOThromb Haemost. 1995;74(1):1.

Actions of Vitamin K

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- **Reversal of the effect of coumarin-like anticoagulants:**normally coumarin-like anticoagulants, which are similar in structure to vitamin K interrupt the vitamin K dependent carboxylation cycle
- **Bone formation:** Vitamin K is a cofactor for some proteins involved in bone mineralization, including osteocalcin (bone Gla protein) and matrix Gla protein
  - Conflicting results of vitamin K replacement on bone loss and BMD

Vitamin K Cycle and Warfarin Metabolism Mayo Clinic Laboratories Communique 2008

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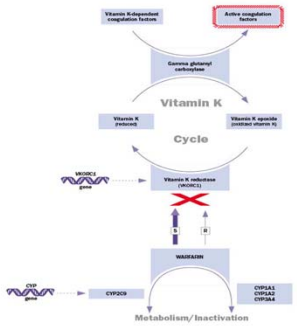

Known gamma-Carboxyglutamic acid-containing proteins

Blood clotting and regulatory proteins	Bone proteins
Prothrombin	Osteocalcin
Factor VII	Matrix Gla protein
Factor IX	**Conopeptides**
Factor X	Conantokin G
Protein C	Conantokin T
Protein S	
Protein Z	
Other proteins	
Gas6	
PRGP1	
PRGP2	

Data reproduced with permission from Furie, B, et al. Blood 1999; 93:1798.

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Symptoms of Vitamin K Deficiency

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- Vitamin K deficiency in an otherwise healthy adult is rare
- **Symptoms**
  - easy bruisability
  - mucosal bleeding
  - splinter hemorrhages
  - melena
  - hematuria
  - any other manifestations of impaired coagulation.

Causes of Vitamin K deficiency

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- Any cause of fat malabsorption
  - Celiac disease, PBC, sclerosing cholangitis, inflammatory bowel disease
- Severe parenchymal liver disease may lead to deficiencies of coagulation factors (alcoholism)
- Medications: warfarin, salicylates, cholestyramine, anticinvulsants
- Antibiotics
  - Diminish gut flora
  - Direct effect on vitamin K activation in the liver
  - Weak coumarin-like effect if vitamin K stores are low

Booth SL, Al Rajabi A. *Vitam Horm*. 2008;78:1-22.

Causes of Vitamin K deficiency..

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- Chronic illness, malnutrition
- Chronic kidney disease, hemodialysis
- Long-term parenteral nutrition
- Massive transfusion
- Severe DIC
- Extremely high doses of vitamin E and A antagonize vitamin K
  - vitamin A reduces vitamin K absorption

Booth SL, Al Rajabi A. *Vitam Horm*. 2008;78:1-22.

Laboratory evaluation

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- Prolonged prothrombin time (PT) and International Normalized Ratio (INR)
- In mild deficiency, only the PT may be prolonged, due to a predominant effect on factor VII
- In severe vitamin K deficiency, both the PT and PTT may be affected
- Measurement of factors V and VII can help to distinguish between liver parenchymal dysfunction and vitamin K malabsorption
- Vitamin K levels can be measured directly but are impractical for clinical use

Vitamin K Replacement

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- Medical therapy for vitamin K deficiency depends on severity of the associated bleeding and underlying disease state
- In life-threatening bleeds, fresh frozen plasma should be administered prior to vitamin K
- If high risk for hematoma formation with im or sc VK administration, then an oral form of VK can be administered

Recommended management of a supratherapeutic INR

INR	Bleeding present	Recommended action*
>Ther to 5.0	No	Lower warfarin dose, **or**
		Omit a dose and resume warfarin at a lower dose when INR is in therapeutic range, **or**
		No dose reduction needed if INR is minimally prolonged
>5.0 to 9.0	No	Omit the next one to two doses of warfarin, monitor INR more frequently, and resume treatment at a lower dose when INR is in therapeutic range, **or**
		Omit a dose and administer 1 to 2.5 mg oral vitamin K1•
>9.0	No	Hold warfarin and administer 2.5 to 5 mg oral vitamin K1. Monitor INR more frequently and administer more vitamin K1 as needed. Resume warfarin at a lower dose when INR is in therapeutic range.
Any	Serious or life-threatening	Hold warfarin and administer 10 mg vitamin K by slow IV infusion; supplement with four-factor prothrombin complex concentrate (4-factor PCC) or fresh frozen plasma, depending on clinical urgency. Monitor and repeat as needed.

INR: International Normalized Ratio; Ther: therapeutic INR range for the patient in question.
* Editor's note: These recommendations, which UpToDate supports, are consistent with the 2008 American College of Chest Physician Guidelines but differ from their 2012 guidelines. Refer to UpToDate text for details.
• This option is preferred in patients at increased risk for bleeding (eg, history of bleeding, stroke, renal insufficiency, anemia, hypertension).
Adapted from: Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; (6 Suppl):160s.

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Thank you