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Meschino Health Comprehensive Guide to Vitamins

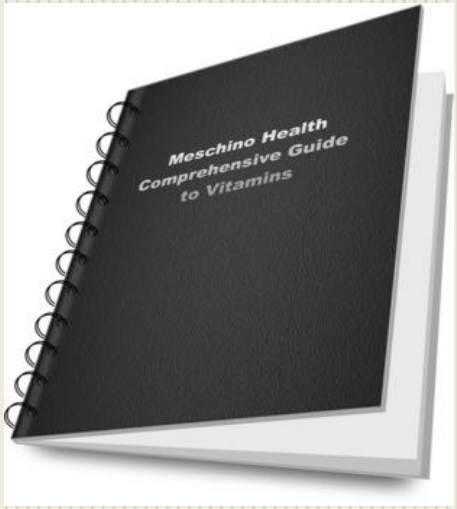

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Table of Contents

About the Meschino Health Comprehensive Guide to Vitamins

The Meschino Health Comprehensive Guide to Vitamins is one of four eBooks on nutrients written by Dr. James Meschino:

1. Meschino Health Comprehensive Guide to Vitamins
2. Meschino Health Comprehensive Guide to Herbs
3. Meschino Health Comprehensive Guide to Minerals
4. Meschino Health Comprehensive Guide to Accessory Nutrients and Essential Oils

All four books were written to both educate and provide an easy to use quick reference to answer important questions regarding nutrients. Users of the guide can quickly find which health conditions the nutrient can impact, proper dosage, possible effects of a deficiency or the effect any potential toxicity associated with the nutrient. Finally any drug-nutrient Interactions associated with the nutrient.

More eBook and eQuick Guides

Meschino Health is excited to be able to provide tools and resources to help you achieve your healthy living objectives. Sharing the Healthy Living message and helping anyone who is interested in living a healthy happy life is what Meschino Health is all about. Visit www.MeschinoHealth.com to learn the latest a science based research on diet and supplementation that can prevent and treat health conditions often associated with aging. New eBooks and eGuides are added every month and can be downloaded free of charge.

Meschino Health Natural Health Assessment

Welcome to the Nutrition, Lifestyle and Anti-aging Assessment.

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- Easy to Complete Online Questionnaire
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- The Meschino Health Assessment is a 15 to 20 page comprehensive report complete with diet, lifestyle and supplement considerations that are specific to your profile.

The Meschino Health Assessment is a free service created by Dr. James Meschino. The feedback in your report is based on your answers to the questions in the Health Assessment, and highlights the dietary, lifestyle and supplementation practices that are best suited to your circumstances, according to currently available scientific studies

The Meschino Health Assessment is a Free Service

Why take it?

We all know that we should eat better, exercise more and change some of our less then desirable lifestyle habits. Did you know that 7 out of 10 North Americans are taking some form of nutritional supplements to augment their diet? While that might sound like good news, the downside is that many people are guessing at what supplements to take! So which one should you take? Better yet, what does eating better look like?

You need a plan.

But where would you even begin to find a health assessment that takes into account your personal health status, diet, lifestyle activities and family health history-before recommending a plan of action?

Where? Right here.

Vitamin A

Dr. James Meschino DC, MS, ND

Introduction

Vitamin A is a vital, but often ignored, nutrient for health optimization and disease prevention. Vitamin A is important to the prevention of cancer, night blindness, and infection. More than 50 percent of Americans do not meet the daily requirement of Vitamin A intake while other Americans ingest excess Vitamin A from supplements, which increases risk of Vitamin A toxicity, birth defects, and osteoporosis. The daily ingestion of Vitamin A is a delicate balancing act between ingesting enough Vitamin A to derive its beneficial effects, while at the same time avoiding over ingestion of this nutrient. This article highlights the important physiological and clinical aspects of Vitamin A that health practitioners should be aware of in regards to making recommendations to their patients about optimizing Vitamin A status and the use of supplements containing Vitamin A.

General Features

Preformed Vitamin A is a fat-soluble group of related compounds. The most common preformed version present in food is retinol; others are retinal (retinaldehyde), and retinoic acid. Retinol can be reversibly oxidized to retinal, which is required for night vision. Oxidation of retinal produces retinoic acid, which does not participate in the visual cycle and cannot be converted back to the aldehyde form (retinal). However, retinoic acid does support growth and normal differentiation of epithelial tissue, but does not support reproductive function, as do other forms of Vitamin A.

In general Vitamin A serves at least five major functions in the body: (1) It helps cells reproduce normally and undergo complete differentiation to fully developed adult cells (cells that have not properly differentiated are more likely to undergo pre-cancerous changes). (2) It is required for vision and one of the first symptoms of Vitamin A deficiency is night blindness. (3) It is required for normal growth and development of the embryo and fetus, influencing genes that determine the sequential development of organs in embryonic development. (4) It may be required for normal reproductive function, with influences on the function and development of sperm, ovaries and placenta. (5) It is a powerful fat-soluble antioxidant. Vitamin A is vital to health optimization and health maintenance as studies show that Vitamin A-deprived animals not only go blind, but also die shortly thereafter. Due to its diverse effects on epithelial cells, including growth, replication, differentiation and antioxidant function, animal studies have shown that Vitamin A reduces the risk of cancer development in epithelial cells in the presence of certain carcinogens.

Absorption and Metabolism

Preformed Vitamin A is absorbed in the gastro-intestinal tract, enters the lymphatic system, within chylomicrons and then the general circulation, which ultimately delivers Vitamin A to the liver, the main storage site (90%) for Vitamin A (also stored to a lesser degree in the kidneys, adipose tissue, and adrenal glands). It is released from the liver in the form of retinol, bound to retinol-binding protein (RBP).

80-90 percent of Vitamin A is typically absorbed from the gut demonstrating excellent bioavailability. Retinoic acid from food is absorbed from the gut and transported in the blood bound to albumin. It normally does not accumulate within the liver or other tissues in any appreciable amounts.

Once delivered to the cells via the bloodstream Vitamin A is extracted from the bloodstream and binds to intracellular proteins within the cell known as CRBP (cellular retinal-binding protein) and CRABP (cellular retinoic acid-binding protein). Within the cells of the body Vitamin A modulates many biochemical reactions, which promote growth, replication, differentiation, and provides additional antioxidant protection.

Functions

Vision

Within the retina, the 11-cis isomer of Vitamin A aldehyde (retinal) is combined with the protein opsin (rhodopsin in the rods and iodopsin in the cones). Light changes the 11-cis configuration to the all-trans form of retinal. This causes visual excitation. When there is a deficiency of Vitamin A, the rods and cones cannot adjust to light changes and night blindness is an early consequence when these cells, especially the rods, are deprived of Vitamin A.

Growth and Bone Development

Through its effects on protein synthesis and differentiation, Vitamin A is necessary for growth and development of bones and soft tissues. It is also required for enamel-forming epithelial cells in the development of teeth. Retinoic acid appears to be the most important form of Vitamin A for these purposes.

Epithelial cell and mucous membrane development and maintenance

Retinoic acid is required for the development of mucous epithelial cells that line the respiratory tract, the alimentary canal, and the urinary tract. Vitamin A deficiency results in “keratinizaton” (drying and hardening) of these tissues, which lowers the protective barrier of these tissues against infection. Sub-optimal Vitamin A status may also render these tissues more susceptible to cancerous changes.

Immune Function

Vitamin A influences both humoral and cell-mediated immunity. The circulating number of T lymphocytes as well as their response to mitogens is reduced in Vitamin A deficiency. Vitamin A is also known as the anti-infective vitamin due to its effects on mucous membranes, helping to create a barrier to infection.

Reproduction

Animal studies provide evidence that retinal is required for normal reproduction and lactation.

Antioxidant

Vitamin A is a potent fat-soluble antioxidant, which appears to have important implications in regards to the prevention of epithelial cancers.

Retinol Equivalents (RE): In addition to preformed Vitamin A, which is present in animal foods, orange-yellow fruits and vegetables and dark green vegetables contain precursors to Vitamin A synthesis, which occurs in the body (e.g. Beta-carotene). In North America, approximately fifty percent of Vitamin A is derived from Vitamin A precursors from the consumption of fruits and vegetables. The following chart outlines the retinal equivalent values of various carotenes as well as preformed Vitamin A.

1 Retinol equivalent	=	1 ug. Retinal
	=	6 ug. Beta-Carotene
	=	12 ug. other provitamin A carotenoids
	=	3.33 I.U. Vitamin A activity from retinol
	=	10 I.U. Vitamin A activity from Beta-Carotene

Vitamin A Recommended Daily Allowance

Group	
Adult males	1,000 Retinol Equivalents (RE)
Adult women	800 RE or 4,000 IU
Pregnancy	1,000 RE (5,000 IU)
Lactation	1,200 RE (2,000-5,000 IU)
Children	400-1,000 RE (2,000-5,000 IU), the amount increasing from infancy to 14 years.

Overt Deficiency of Vitamin A

1. **Night Blindness (Nyctalopia)**
2. **Xerophthalmia or Xerosis Conjunctivae**

   This progressive disorder of the eye leading to blindness involving dryness, thickening, wrinkling and pigmentation of the conjunctiva, Bitot's spots, dryness and keratinisation of the cornea and finally ulceration, softening of the cornea and possibly perforation and iris prolapse and infection.
3. **Follicular Hyperkeratosis (Toad Skin)**

   Goose flesh appearance known as Xeroderma. In follicular hyperkeratosis, the hair follicles are blocked with plugs of keratin from the epithelial lining. The result is rough, dry, scaly skin beginning with the forearms and thighs and progressing to full-body involvement.
4. **Other:**
   growth inhibition
   skeletal abnormalities
   decreased resistance to infection
   taste bud keratinisation and loss of sense of taste
   loss of appetite[1]

Comment [O1]: Jim is this a mistake should it be part of the first line.

The North American Vitamin A Status Update

The National Health and Nutrition Examine Surveys (I and II), along with the Continuing Survey of Food Intakes by Individuals and 1994-96 Diet and Health Knowledge Survey (ARS Food Surveys Research Group. Internet – 1997), indicate that approximately 56 percent of Americans do not meet the daily requirement for Vitamin A intake. In fact, in many cases individuals only consume 50% of the RDA level on a daily basis. Thus, marginal deficiency of Vitamin A is not uncommon in developed countries. As such, the use of a multiple vitamin supplement each day providing 2,500-3,000 IU of preformed Vitamin A and 10,000-15,000 IU of beta-carotene may be highly beneficial to health optimization and the prevention of epithelial cancers according to epidemiological studies, and experimental data. However, consuming a multiple vitamin containing 5,000 IU or more of preformed Vitamin A, may increase risk of Vitamin A toxicity over the long-term, increase risk of osteoporosis in postmenopausal women, and may increase risk of birth defects. On the other hand, there are special cases where higher doses of Vitamin A can be used on a therapeutic basis, but higher doses require proper monitoring for Vitamin A toxicity and should not be used during pregnancy, lactation or by individuals with liver or kidney disease.

Vitamin A Toxicity

Toxicity has been associated with abuse of Vitamin A supplements and with diets extremely high in preformed Vitamin A. Consumption of 25,000-50,000 IU/d for periods of several months or more can produce multiple adverse effects. Individuals at highest risk have liver function previously comprised by drugs, viral hepatitis, alcohol, or protein-energy malnutrition.

Children - adverse effect have been shown to occur with intakes as low as 1,500 IU/kg/day.

Pregnant women - increased risk of birth defects has occurred with maternal intakes as low as 25,000 IU/day.

From a clinical standpoint, Vitamin A toxicity typically occurs in patients taking high dose Vitamin A (≥ 50,000 IU) for various skin conditions (e.g. acne, psoriasis, eczema). Even synthetic water-soluble Vitamin A has been shown to cause toxicity at doses of 18,500 to 60,000 IU per day over a period of months.

Signs and Symptoms of Vitamin A Toxicity	
Children	**Adults**
Anorexia Bulging fontanelles Drowsiness Increased intracranial pressure Irritability Vomiting	Abdominal pain Anorexia Blurred vision Drowsiness Headache Hypercalcenia Irritability Muscle weakness Nausea, vomiting Peripheral neuritis Skin desquamation Brittle nails Cheilosis Gingivitis Alopecia
Birth defects associated with high maternal intake of Vitamin A (18,000-100,000 IU before and throughout pregnancy): Abnormalities of the head, face, ears, eyes, mouth, lips, jaw, heart and urinary system: other defects[2]	

Vitamin A dosages greater than 10,000 IU during pregnancy (specifically the first 7 weeks after conception) have probably been responsible for one out of 57 cases of birth defects in the United States. Women who are at risk for becoming pregnant should keep their supplemented Vitamin A levels below 5,000 IU per day.3 A study showed that

59 women taking prescription Vitamin A 13-cis retinoic acid (Accutane) for acne, who became pregnant resulted in 12 spontaneous abortions and 21 malformed infants.

Vitamin A Supplementation

Acute Viral Infection 50,000 IU for one or two days

Cancer Treatment and Prevention

Wolback and Howe noted that retinoid-deficient epithelial tissues had a premalignant phenotype (appearance) that was characterized by enhanced mitotic activity (rapid cell turnover) and loss of differentiation.4

Retinoids are known to possess antiproliferative, differentiative, immunomodulatory and apoptosis-inducing properties. A growing body of evidence supports the hypotheses that the retinoic acid receptor B2 gene is a tumor suppressor gene, and that the chemopreventive effects of retinoids are due to induction of this receptor.5 A unique Vitamin A compound is presently being used in cancer prevention and treatment. This form of Vitamin A, known as 9-cis-retinoic acid, has been used to suppress premalignant oral lesions and prevent the development of secondary primary cancers among patients with head and neck and lung cancers. This form of Vitamin A is now being considered in the treatment of breast cancer, which often displays under expression of the retinoic acid receptor B2.6-9

Note that a number of alternative practitioners and holistic medical practitioners often recommend high doses of water soluble Vitamin A (50,000-300,000 IU per day) as part of the adjunctive nutritional support for patients with certain cancers. Many of these practitioners suggest it is a useful intervention to help prevent recurrence of certain cancers and control the spread of existing lesions (www.diagnoseme.com). In these cases, monitoring for Vitamin A toxicity is mandatory.

Acne

There is some evidence that Vitamin A supplementation at 25,000 IU per day may improve acne. However, this dose may lead to signs of toxicity (headache, cracking and chapped lips, fatigue, dry skin, and joint pain are early warning signs and symptoms). A dose above 5,000 IU per day also increases the risk of birth defects in children born to mothers ingesting these higher levels of Vitamin A at the time of conception.10

In my experience, a safer and more appropriate natural treatment for acne is the ingestion of the P73 Wild Oregano Capsules in conjunction with topical application overnight of the P73 Wild Oregano Cream. This form of wild oregano has been shown to kill many bacteria, viruses and fungi, which appears to include the bacteria involved in acne.

Drug-Nutrient Interactions

Bile acid sequestrants such as cholestyramine and colestipol, are known to reduce Vitamin A absorption.[11,12]

Neomycin is known to reduce the absorption of Vitamin A and increase its excretion, which increases need for Vitamin A supplemention.[13]

Mineral oil decreases the absorption of Vitamin A.[14]

Vitamin A-derivative drugs (isotretinoin) may increase risk of toxicity by potentiating the effects of Vitamin A. Caution should be exercised with respect to Vitamin A supplementation in these cases.[15]

Orlistat decreases Vitamin A levels in the body which increases demand for Vitamin A supplementation.[16,17]

Corticosteroid drugs may decrease Vitamin A levels in the body, which increases demand for Vitamin A supplementation.[18]

High doses of Vitamin A may impair the absorption of Vitamin E if taken concurrently.[19]

Pregnancy and Lactation

1. During pregnancy and lactation, the only supplements that are considered safe include standard prenatal vitamin and mineral supplements. All other supplements or dose alterations may pose a threat to the developing fetus and there is generally insufficient evidence at this time to determine an absolute level of safety for most dietary supplements other than a prenatal supplement. Any supplementation practices beyond a prenatal supplement should involve the cooperation of the attending physician (eg., magnesium and the treatment of preeclampsia.)

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Beta-Carotene

Introduction

Beta-Carotene is one of 30-50 carotenoids found in plant foods that can be converted by the body into Vitamin A. Beta-Carotene is a fat-soluble compound that is absorbed intact in the presence of bile salts from the intestine. Beta-Carotene is made up of two Vitamin A molecules (attached together). Within intestinal cells they are split to yield retinol (preformed Vitamin A). Approximately one third of all the carotene in food can be converted into Vitamin A. For Beta-Carotene specifically, about one-sixth is available to become Vitamin A, if the body requires it.

Absorption and Metabolism

The splitting of Beta-Carotene (and other carotenes) into retinol within intestinal cells is well regulated to help guard against Vitamin A toxicity. The retinol that is formed from Beta-Carotene enters the chylomicron and is metabolized from that point forward as preformed Vitamin A. Chylomicrons primarily deliver Beta-Carotene to the liver, where they are repackaged within another lipoprotein carrier system known as the very-low-density lipoprotein.

Beta-Carotene (and other carotenoids) enters the bloodstream from the liver and is transported to peripheral tissue by very-low density lipoproteins and low-density lipoproteins (VLDL and LDL, which is the remnant particle of VLDL after triglycerides are removed by fat cells, muscle fibers and other tissues). In contrast, Vitamin A is transported form the liver attached to retinal-binding protein (RBP). Beta-Carotene is stored in fat tissues, and the adrenal glands, testes, ovaries, rather than the liver and is responsible for the yellowish tinge to the skin when large amounts are stored (carotenodermia). However, carotenodermia is considered to be a nonpathological, reversible condition; not associated with any health risks. Some conversion of Beta-Carotene may take place in the liver and lungs. About 40-60% of Beta-Carotene is absorbed from food. Of interest is the fact that Beta-Carotene supplements are better absorbed than carotenes from food. Beta-Carotene comprises 20-25% of the total serum carotene level.

Functions

Vitamin A Precursor: because Beta-Carotene can be converted into Vitamin A, it supports Vitamin A nutritional status and all vitamin A-related functions.

Antioxidant: Beta-Carotene is an antioxidant and does not need to be converted into Vitamin A to perform antioxidant functions.

Immune System: Beta-Carotene appears to enhance thymus gland function and increases interferon's stimulatory action on the immune system.[1]

Other Functions: as described below, Beta-Carotene exhibits a number of immune-enhancing and anti-cancer propertied, and has therefore, been tested in patients with immune-compromised states, precancerous, and cancerous conditions, as well as in patients at high risk in developing certain cancers.

Beta-Carotene Supplementation

Compromised Immune Function

A number of studies reveal that older subjects can enhance various aspects of immune function through the supplementation of at least 15 mg of Beta-Carotene (25,000 I.U.) per day. The immune system tends to weaken as humans age, thus researchers have examined various nutrients that may prevent or reverse age-related decline in immune function. High doses of Beta-Carotene have been used in the treatment of immune compromised states and studies on normal human volunteers indicate that supplementation with 180 mg (300,000 I.U.) of Beta-Carotene per day, significantly increased in the number of T-helper cells by approximately 30% after seven days of supplementation, with a 30% increase in a total T-cell count after 14 days. This may be of great significance in HIV/AIDS patients, who have low T-helper cell counts and other parameters of immune function compromise.[2-5] Beta-Carotene supplementation at 50,000 I.U., twice per day administered to AIDS patients has resulted in a 66% rise in total lymphocyte count and a small rise in T-helper cell levels. With discontinuation of Beta-Carotene supplementation, lymphocyte and T-helper cell counts returned to base line levels within six weeks.[2] In a second study, 60 mg (100,000 I.U.) administered to seven AIDS patients resulted in a rise of T-helper cells over the four-week trial period. This is important as it is the T-helper cell (CD$) count that is adversely affected by the HIV virus and largely accounts for the dramatic reduction in immune function seen in HIV and AIDS patients.[27] Not all Beta-Carotene studies with AIDS patients have shown these benefits, but the lack of adverse side effects with Beta-Carotene suggests that it can be used safely as a complementary therapy in these cases.[2] Moderate dosages of Beta-Carotene supplementation may help to slow down or halt the age-related decline in immune function that increases susceptibility to infection and possibly cancer, as we age. This is true as well for other antioxidant vitamins (Vitamin C, Vitamin E, Vitamin A) and the minerals zinc and selenium.[3,4,5]

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Cancer Prevention

At this time it is inadvisable to give high dose Beta-Carotene supplementation (50,000 I.U. or greater) to patients who smoke one pack of cigarettes per day or more. The Alpha-Tocopherol, Beta-Carotene study and the CARET study suggested that Beta-Carotene, in these cases, may slightly increase the risk of lung cancer, although this needs confirmation.[6,7] However, Beta-Carotene does demonstrate a number of anti-cancer properties and has been shown to reverse leukoplakia – a pre-cancerous condition of the oral cavity, as well as early-stage cervical dysplasia, a pre-cancerous condition of the uterine cervix.[8-13] In the Linxian China study, the combination of modest dosages of Beta-Carotene, Vitamin E, and selenium significantly reduced stomach and esophageal cancers, as well as total cancer incidence in high-rish individuals, compared to other vitamin and mineral combinations.[26] Beta-Carotene is an antioxidant, an immune system modulator and enahances cellular differentiation of epithelial cells. All of these effects are associates with the prevention of cancer and the reversal of some early stage cancers and states of dysplasia (pre-cancerous states).[4-13]

Cervical Dysplasia

Beta-Carotene has been shown to influence cellular differentiation of surface lining cells (epithelial cells) and enhances immune-system function. Beta-Carotene has been shown to halt the progression of cervical dysplasia and cause a reversal in some cases involving early and moderate stages of this condition, which is known to be a pre-cancerous condition.[12,13,18]

Cardiovascular Disease

Beta-Carotene supplementation has been shown to decrease oxidation of LDL-cholesterol, but to a lesser degree than Vitamin E. In this regard, it may help to reduce the risk of cardiovascular disease, as oxidized LDL-cholesterol appears to be more inclined to narrow arteries as part of the atherosclerotic process that leads to heart disease and ischemic stroke. However, evidence is stronger for Vitamin E. Both Vitamin E and Beta-Carotene are transported through the bloodstream within VLDL and LDL lipoproteins, where they are able to act as antioxidants in regards to reducing the oxidation of fatty acids and cholesterol within these lipoproteins (VLDL and LDL).[14,15,16] The Physicians Helath Study failed, to show a benefit in cardiovascular disease reduction with Beta-Carotene supplementation of 50 mg (83,333 I.U.), taken every other day for 12 years. However, a subgroup analysis of these 22,000 medical doctors showed that of the 333 physicians prior history of heart disease, Beta-Carotene supplementation produced a small reduction in risk of fatal and non-fatal heart attack.[30] A number of prospective studies have suggested that higher intakes of Beta-Carotene is associated with a significant reduction in heart attack and stroke, as highlighted in the Western Electric Study in Chicago and a study of Italian women by A Tavani, et al.[28,29]

Dosage

1. Compromised Immune Function: 50,000 I.U., but a dosage of up to 3,000,000I.U. has been used in short term studies[2-5]
2. HIV/AIDS: 50,000 I.U., twice daily has been used with some success[2,27]
3. Oral Leukoplakia: 50,000-1000,000 I.U. per day[9,10]
4. Cervical Dysplasia: 50,000-100,000 I.U. per day[12,13]
5. Cancer Treatment Support: 75,000-100,000 I.U. per day (lung cancer would be an exception)[11]
6. Heart Diseases and Cardiovascular Health: 10,000-75,000 I.U.[14,30]
7. General Wellness: 10,000-25,000 I.U. is commonly consumed

Adverse Side Effects and Toxicity

Overall, the experimental animal data demonstrate a high level of Beta-Carotene safety and in human trials using doses of 20-180 mg/d (up to 300,000 I.U./d) to treat patients with the genetic disease erythropoietic protoporphryria. These large doses did not produce any toxic effects. Other studies have confirmed this. Babies born to mothers with carotenemia show no untoward effects or defects and are otherwise normal.[17]

Drug-Nutrient Interactions

Bile Acid Sequestrants, such as cholestyramine and colestipol may decrease absorption of Beta-Carotene (as they do other fat-soluble vitamins).[19,20]

Proton Pump Inhibitors such as omeprazole are known to decrease Beta-Carotene absorption.[21]

Other drugs that impair Beta-Carotene absorption include:

colchicines[22]

mineral oil[23]

neomycin[24]

orlistat[25]

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Lycopene

Introduction

Lycopene, the carotenoid that provides the red colour to tomatoes and watermelon, concentrates in the male prostate gland where it is thought to act as an antioxidant and provide other protective effects against prostate cancer. Lycopene represents as much as 50% of the carotenoids found in human serum. Lycopene demonstrates a high level of bioavailability, which is enhanced when tomatoes and other lycopene-containing vegetables and fruits are heated, chopped and processed. This explains why tomato sauce is such a good and bioavailable source of lycopene. Lycopene has been shown to concentrate in the prostate gland, adrenals, testes, skin, liver and kidneys. The body cannot convert lycopene into Vitamin A, as it can with some other carotenoids (e.g. beta-carotene), but lycopene demonstrates powerful antioxidant activity and is the most effective quencher of oxygen free radicals among the many carotenoids found in nature, being twice as potent as beta-carotene in this regard. In addition to its role as an antioxidant lycopene demonstrates a number of other anti-cancer properties. Under experimental conditions lycopene is able to reduce lung adenomas and carcinomas, colon cancer, prostate cancer, breast (mammary) tumor, and to inhibit endometrial cancer as well as HL-60 leukemic cell growth.
Epidemiological evidence indicates that the ingestion of tomato products is associated with a reduction in risk of overall cancer mortality or incidence. The evidence appear to be strongest for reduced risk of pancreatic, rectal, colon, esophageal, oral, cervical, breast and prostate cancer. The Mediterranean-type diet in particular, which has a higher intake of tomato products, is associated with lower incidence of digestive tract cancers.

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Prostate Cancer

Lycopene intake of 6.5 mg per day has been linked to a 21% decreased risk of prostate cancer compared with those consuming the least. This study also reported that those who ate more than ten servings per week of tomato-based foods had a 35% decreased risk of prostate cancer compared with those eating less than 1.5 weekly servings.[1]

Lycopene is the most abundant carotenoid in the prostate[2], and high blood levels of Lycopene have been linked to prostate cancer prevention,[3] including prospective or longitudinal studies.[4]

Women's Health

Higher intakes of Lycopene have also been associated with a lower risk of cervical intraepithelial neoplasia – precancerous changes of the cervix and cervical dysplasia.[5-8] Some preliminary evidence also suggests that Lycopene may help reduce the risk of breast cancer.[9]

Cardiovascular Disease

Observational and experimental studies also suggest that Lycopene may reduce risk of heart disease (up to 48% lower risk reported).[10] Lycopene may reduce LDL-C oxidation, inhibit cholesterol synthesis in the liver, or enhance LDL degradation.[11] Intervention trials are required to see if Lycopene can prevent cardiovascular disease to the degree suggested by these observational and experimental studies.

Cancer in General

Lycopene may help to reduce risk of cancer through its antioxidant function, immune modulating effects and/or its antiproliferative influence. Recent studies have shown that high insulin-like growth factor I (IGF-I) blood levels is a risk factor in breast and prostate cancer. Lycopene has been shown to reduce IGF-I stimulation leading to an antiproliferative effect on various cancer cell lines including breast, endometrial and lung.[12,13]

Immune System

Lycopene supplementation has also boosted immune function in the elderly (15 mg of Lycopene per day increased natural killer cell activity by 28% in twelve weeks).[14]

Adverse Side Effects and Toxicity

No reports of toxicity have been reported to date with Lycopene supplementation.[14,15]

Drug Nutrient Interactions

The following drugs are reported to decrease the absorption of Lycopene and thus, should not be ingested at the same time as Lycopene:

Mineral Oil[16]

Orlistat[17,18,19]

Bile Acid Sequestrants[20,21]

Olestra containing products[22,23]

Chitosan[24]

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Lutein & Zeaxanthin

Introduction

Lutein and Zeaxanthin – these two carotenoids are found in high levels in dark-green leafy vegetables and are known to concentrate in the macula of the eye. They have been shown to play a role in the prevention and treatment of macular degeneration and, more recently, retinitis pigmentosa.

Macular Degeneration and the Role of Lutein and Zeazanthin:

The macula, especially the central portion (the fovea), within the retina of the eye, owes its yellow colour to its high concentration of Lutein and zeazanthin. These yellow carotenes, although not a source of Vitamin A, function as an antioxidant, prevent oxidative damage to the area of the retina responsible for fine vision and play a role in the prevention of macular degeneration - the leading cause of severe visual loss in North America and Europe, in persons aged fifty-five years and older.[1]

There is strong evidence that Lutein and zeazanthin reduce the risk (up to 57%) of age-related macular degeneration and may help to stabilize this condition.[2] Lutein may also help to prevent cataracts.[3]

Some authorities recommend an antioxidant combination of supplements to help treat macular degeneration. Generally, 5 mg of Lutein plus 50,000 I.U. of mixed carotenoids are included in this protocol.[4] Lutein supplementation studies have shown that macular pigment increases by an average of 5.3% after 4 weeks of supplementation with 10 mg of Lutein.[5] Zeazanthin supplementation is typically included at 1 mg per day, but it should be noted that Lutein can be converted to zeazanthin in the retina.

Other studies using Lutein supplementation have also revealed significant increases in macular pigment.[6]

A study of 13 patients with retinitis pigmentosa and 3 patients with macular degeneration, demonstrated significant improvement when subjects were given 40 mg of Lutein supplementation for 9 weeks, followed by 20 mg/day thereafter. The trial lasted 26 weeks in total. The findings of this study showed that patients with retinitis pigmentosa experienced significant improvement in both their visual acuity and visual field area within the first four weeks of Lutein supplementation. Blue-eyed subjects reported more dramatic results, in terms of visual acuity from Lutein supplementation than did dark-eyed individuals. Individuals also taking Vitamin A and/or Beta-carotene benefited more than others in terms of visual acuity improvements. Dark-eyed individuals do not appear to increase their macular pigment from supplements as much as blue-eyed people, according to this and previous studies, which may imply that these individuals have a lesser need for this nutrient than do blue-eyed individuals, in order to protect the macular region of the eye from damage induced by blue light.[7]

In the same study, the 3 patients with macular degeneration, also demonstrated significant improvement upon ingesting 40 mg of Lutein supplementation for 9 weeks, followed by 20 mg/day thereafter. The trial lasted 26 weeks in total.[7]

A large number of experimental investigations demonstrate that age-related macular degeneration is caused by, or in some way promoted by, free radical damage from sunlight (uv-light, especially blue light) and cigarette smoking. Higher dietary and supplemental intake of Lutein and zeazanthin have been shown to result in increased concentrations of these nutrients in the macula, where they absorb damaging blue light, helping to intercept and neutralize free radical damage, and reduce the risk of macular degeneration.[8-13] For example, in a 140 day study involving two individuals, who consumed 30 mg of free Lutein per day, macular pigment optical density increased 39% in one subject and 21% in the other subject. This change in macular pigment optical density was estimated to reduce

the amount of damaging blue light reaching the photoreceptors, Bruch's membrane, and the retinal epithelium (the vulnerable tissues affected by age-related macular degeneration), by 30 to 40%.[6]

Dosage

The average intake of Lutein from food each day ranges from 0.6 to 0.8 mg, but half a cup of cooked spinach, kale, or broccoli adds from 1.2 to 10 mg of Lutein to the diet.[24]

Many health experts recommend about 6 mg of Lutein per day as part of a supplementation program for the management of various eye conditions (e.g., macular degeneration, cataracts, retinits pigmentosa).[25,26] However, studies using 20 and 40 mg of Lutein supplementation have demonstrated impressive results in these cases without producing any apparent adverse side effects over a five to six-month period.[6,7]

Adverse Side Effects and Toxicity

No reports of toxicity have been reported to date with Lutein or Zeazanthin supplementation at the above noted levels.[6,7,14]

Drug-Nutrient Interactions

The following drugs are reported to decrease the absorption Lutein and, thus should not be ingested at the same time.
Orlistat[15,16,17]
Mineral oil[18]
Bile Acid Sequestrants[19,20]
Olestra - containing products[21,22]
Chitosan[23]

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Vitamin B_1 - Thiamine

Introduction

The B-Vitamins play an essential role in the metabolic processes of all living cells by serving as cofactors in the various enzyme systems involved in the oxidation of food and production of energy. Some B-Vitamins are required for DNA synthesis, the formation of myelin, neurotransmitters, creatine, red blood cells and participate in other vital functions, such as maintaining safe blood levels of homocysteine.

Vitamin B_1, or Thiamine, is known as the antineuritic vitamin because it is needed for normal functioning of the nervous system.

Absorption and Metabolism

Thiamine is absorbed in the proximal and lower duodenum. It is phosphorylated in the mucosal cell to Thiamine phosphate and then carried to the liver by the portal circulation. It is not stored in any great quantity in the body and must, therefore, be supplied daily.

Functions

Energy metabolism

Thiamine combines with phosphorus to form the coenzyme Thiamine pyrophosphate (TPP), which is necessary to convert pyruvate to acetyl coenzyme A, the central compound of the Kreb's cycle. The Krebs cycle yields ATP energy to power all biological reactions within the body.

Synthesis of Nucleotides and Fatty Acids

TPP is required in the pentose phosphate shunt, which is necessary to synthesize nucleotides, required to make DNA and RNA, and for fatty acids.

Nerve conduction

TPP affects the nerve cell membrane in a manner that facilitates normal nerve transmission. This is a non-coenzyme function of Thiamine.

Recommended Dietary Allowance (Vitamin B_1/Thiamine)

RDA Thiamine	0.7-1.0 mg. per day
Adults (1.0-1.5 mg)	1 mg per day
Pregnancy	1.4 mg per day
Lactation	1.6 mg per day
Infants under 6 months	0.3 mg per day
6-12 months	0.4 mg per day
Ages 1 to 10 years	(progressive increase)

Classical Vitamin B_1 Deficiency

1. **Beriberi**

   Beriberi is a condition that affects the nervous system and/or the heart muscle. Lack of ATP synthesis in Vitamin B1 deficiency (Beriberi) results in loss of function or paralysis of the lower extremities (polyneuritis) and/or heart failure. In modern society, it is most common in alcoholics.

2. **Wernicke-Korsakoff Syndrome**

   This is a syndrome often found in alcoholics, includes encephalopathy, with loss of immediate memory, disorientation, nystagmus and/or ataxia, as well as signs and symptoms of polyneuritis and related B1 deficiency signs and symptoms.1

Vitamin B1 Supplementation

1. **Epileptics taking Dilantin**

   Typically experience improved mental function has been noted in these subjects with 50 mg Thiamine supplementation in a six-month trial.[2]

2. **Alzheimer's Disease**

   Many Alzheimer's Disease patients have been shown to have poor B_1 nutritional status.[3] Thiamine demonstrates some pharmacological effects on the brain in that it mimics acetylcholine, the memory neurotransmitters.[4] Thiamine has been shown to improve mental function in patients with Alzheimer's Disease and age-related impaired mental function (senility) at a dose of 3 to 8 grams per day. The long-term consequences of a dose this high is unknown at this time, but no significant side effects have been reported in these preliminary trials.[5,6]

3. **Congestive Heart Failure**

   Older individuals often display poor nutritional status for Vitamin B_1. Many diuretic drugs used for high blood pressure and congestive heart failure cause a depletion of Thiamine, which is needed for energy production in heart muscle.[3,7] In a trial supplementing patients with congestive heart failure with 80-240 mg of Thiamine, there was an increase in left ventricular ejection fraction of 13 to 22 percent, on average. This outcome is associated with improved survival.[8]

4. **Mouth Ulcers (Cankers or Apthous Stomatitis)**

   Supplementing with 300 mg B_1, 20 mg B_2 and 150 mg B_6 has been reported to provide relief in people suffering from regular outbreaks of canker sores. Thiamine deficiency is strongly linked to apthous ulcer vulnerability.[9,10]

5. **Depression**

   Deprivation of Thiamine (0.33 mg per day) results in signs of depression, fatigue, headaches, including voluntary restriction of social engagements. Symptoms were alleviated when subjects were given 1.4 mg of Thiamine for only one day in one study.[11]

Vitamin B1 Toxicity

Thiamine appears to be very non-toxic even at high levels of intake $\geq$ 100 mg per day.[11,12]

Drug-Nutrient Interactions

1. **Alcohol**

   Alcohol interrupts the conversion of Thiamine to its active form, which can result in Vitamin B_1 deficiency with excessive intake.[13]

2. **The following drugs are also reported to cause Thiamine depletion:**

   Antibiotics: decrease B_1 synthesis by bacterial flora[14,15]

   Loop Diuretics: cause increased urinary loss of Thiamine[16]

   Oral Contraceptives[17]

   Phenytoin (anti-seizure drug)[8]

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Vitamin B_2 - Riboflavin

Introduction

Riboflavin is a yellow-green fluorescent pigment that is responsible for the bright yellow urine that accompanies supplementation with this B-vitamin.

Absorption and Metabolism

Riboflavin is easily absorbed in the proximal small intestine. Only 15% is absorbed when taken alone and 60% of a 30 mg dose is absorbed when taken with food. It is phosphorylated to flavin mononucleotide (FMN) in the intestinal cells, and then carried into the bloodstream. The amount of riboflavin stored in the liver and kidneys is minimal, and therefore, it must be regularly supplied in the diet.

Functions

Energy Metabolism: in the form of FMN and FAD, these derivatives of Vitamin B_2 are the prosthetic group of flavoproteins, involved in energy production within the mitochondria of the cell. They catalyze the first step in oxidative phosphorylation to help generate ATP energy.
Glutathione Formation
Steroid synthesis and amino acid metabolism
Red Blood Cell Production
Activates Vitamin B_6 and folic acid: acts as a coenzyme to convert Vitamin B_6 and folic acid to their active biological forms in the body.

Classical B2 Deficiency

Growth retardation: severe deficiency

Cheilosis: cracks at corners of the mouth

Glossitis: smooth and purplish tongue

Inflamed mouth

Dry, scaly facial skin

Seborrheic dermatitis, especially the nose-labial folds[1]

Low levels linked to esophageal cancer[2]

Recommended Daily Allowance (Vitamin B_2)

Age Group and Gender	Vitamin B_2 (mg)
Healthy adults	1.5-1.8
Pregnancy	1.6
Lactation	1.8
Infants (<6 months)	0.4
Infants (6-12 months)	0.5
Children 1-10 years	0.8-1.2 (progressive intake)[1]

Riboflavin Supplementation (above RDA)

Migraine Prevention

49 migraine patients were treated with 400 mg of Riboflavin for at least 3 months. A 68.2 percent improvement in frequency and duration of headache was reported in this group. The researchers indicated that there were no serious side effects from B_2 treatment at this dosage and the treatment was well tolerated and effective.[3]

Cataract Protection

In one trial of Chinese subjects known to have sub-optimal intakes of Vitamin B_2, older individuals supplemented with 3 mg of Vitamin B_2 and 40 mg B3 per day demonstrated partial protection against cataracts.[4]

Mouth Ulcers (Apthous Stomatitis)

Supplementing with 300 mg Vitamin B_1, 20 mg Vitamin B_2 and 150 mg Vitamin B_6 has been reported to provide relief and faster healing in some people.[5]

Adverse Side Effects and Toxicity

No toxicity or side effects from Riboflavin supplementation have been demonstrated.[6,7]

Drug - Nutrient Interactions

1. **Tricyclic Antidepressants**
   Animal studies report that these drugs reduce the conversion of Riboflavin to its active form (e.g. amitriptyline, imipramine), which may increase Vitamin B_2 requirement.[8]

2. **The following drugs are reported to cause riboflavin depletion:**
   Antibiotics: antibiotics reduce B-vitamin synthesis by bacterial flora[9,10]
   Oral contraceptives[11,12]
   Chlorpromazine: animal studies indicate that this drug increases Riboflavin elimination[13]

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Vitamin B_3 – Niacin (Nicotinic Acid)

Introduction

Niacin (nicotinic acid), like riboflavin, is directly involved in the production of energy at the cellular level enabling the body to convert carbohydrate, fat, and protein into ATP energy. Niacin, in the form of NAD, transfers hydrogen molecules from these sources to riboflavin (FMN), which in turn transfers hydrogen in a stepwise fashion to the cytochromes within the mitochondria. These transfers allow parcels of energy to be released which re-couples ADP with inorganic phosphate to form more ATP – the ultimate source of energy to power biological reactions in the body. Niacin, which occurs naturally as nicotinic acid, is easily converted by the body to its active form, nicotinamide. It is frequently administered as nicotinamide for therapeutic reasons, since nicotinic acid acts as a vasodilator and can produce severe flushing and itching. Because the body can convert tryptophan (an amino acid) into niacin, some nutritionists do not consider Niacin to be an essential dietary nutrient as along as tryptophan intake is adequate. Approximately 60 mgs of dietary tryptophan can be used to synthesize 1 mg of Niacin in the body. It is involved in more than 200 enzyme reactions and is essential for healthy skin, tongue, digestive tract cells, and the formation of red blood cells.

Absorption and Metabolism

Niacin is absorbed in the small intestine. Little storage occurs in the body and, therefore, it must be supplied regularly.

Functions

Energy Production

Nicotinamide functions in the body as a component of the coenzymes NAD (nicotinamide adenine dinucleotide) and NADH (nicotinamide adenine dinucleotide phosphate). NAD and NADH accept and release hydrogen atoms derived from carbohydrates, protein and fat, in the energy production pathway (oxidative phosphorylation), to facilitate the production of ATP energy.

Synthesis of fatty acids and cholesterol

NADH is necessary in the synthesis of fat from acetylcoenzyme A (Acetyl CoA), which commonly occurs in the liver after over-ingestion of carbohydrates (many excess carbohydrate molecules are converted to Acetyl CoA in the liver).

Glycogen synthesis

NAD is required to store carbohydrates as glycogen in the liver and skeletal muscles.

Recommended Daily Allowance (Vitamin B3)

Group		Milligrams
Infants		
	Under 6 months	5
	6-12 months	6
Children		
	1-3 years	9
	4-6 years	12
	7-10 years	13
Young Adults and Adults		
Males	11-14 years	17
	15-18 years	20
	19-50 years	19
	51+ years	15
Females	11-50 years	15
	51+ years	13
Pregnancy		17
Lactation		20

Classical Niacin Deficiency

Pellagra

Dietary levels of less than 7.5 mg per day of niacin, or niacin-equivalents from tryptophan, have been associated with the production of pellagra. Pellagra manifests as Dermatitis, Dementia, Diarrhea (the 3 Ds of pellagra) as well as tremors, sore tongue (beef tongue), and inflamed mouth. Other signs and symptoms include cracked, pigmented scaly dermatitis in body parts exposed to sunlight, anxiety, depression, and dementia.[1]

Niacin Supplementation

1. Lowering Blood Lipids

Studies have shown that Niacin supplementation at 1,500-4,500 mg per day can reduce LDL-cholesterol by up to 23%, increase HDL-cholesterol by up to 33% and reduce LP(a) lipoprotein by up to 35%. However, high doses of Niacin in various forms can damage the liver. Thus, only practitioners who can monitor liver enzyme and function tests should recommend or prescribe Niacin for hyperlipidemic patients.[2] Some studies indicate that the safest of this form of Niacin is inositol hexaniacinate.[3] However, the amount of research studying the safety of this form of Niacin remains quite limited. Risk of liver damage begins with intakes of Niacin at or above 1,000 mg per day.[4]

2. Osteoarthritis

Niacin supplementation has been shown to improve global arthritis symptoms by 29% vs placebo (10% worse). Parameters included joint flexibility, inflammation and decreased reliance upon other anti-inflammatory medications.[5]

3. Defends Skin Against UV-light Damage

Experimental evidence demonstrates that Niacin supplementation reduces UV-light-induced damage to the DNA of skin cells and protects against photo-aging of the skin. Niacin increases cellular ATP energy required by skin cells to repair the free radical damage imposed by UV-light exposure and bolsters immune function of the skin under test conditions. As such, Niacin supplementation (50-100 mg per day), in conjunction with antioxidant supplementation (Vitamins C, E, Selenium, Beta-Carotene) is emerging as a factor that may help to reduce risk of skin cancer and premature aging of the skin. [6,7,8,11,12,13]

Niacin Toxicity

A high dose of niacin, above 1,200 mg per day, which has been used to treat high cholesterol, increases the risk of liver damage. If continued long enough, it may aggravate diabetes by affecting glucose metabolism and can activate ulcers.[9]

Doses in excess of 50 mg of Niacin (nicotinic acid) but not nicotinamide, typically produce a transient flushing of the skin, due to its vasodilatory effects.[10]

Niacin supplemented at 100-1,000 mg without concurrent supplementation of folic acid and VitaminB_{12}, can result in an elevation of homocysteine (17%), which may increase risk of heart disease.[11]

Contraindications

Diabetes: Niacin dosage should not exceed 100 mg, per day.

Pre-existing Liver Disease: Niacin dosage should not exceed 100 mg, per day

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Gout: Niacin dosage should not exceed 50 mg, per day. Nicotinic acid competes with uric acid for excretion in the urine. As such, high intakes of nicotimic acid can impair the excretion of uric acid, aggravating symptoms of gouty arthritis.

Peptic Ulcers: Niacin dosage should not exceed 50 mg, per day.[10,11,12]

Safe Intake Level for Nutritional Support: 20-100 mg per day of Niacin is considered a safe level of supplementation for individuals 11 years of age and older, unless contraindications are present.[13]

Drug-Nutrient Interactions

The following drugs are reported to cause Niacin depletion:

Antibiotics

Antibiotics reduce B-Vitamin synthesis by destroying gut bacteria, which synthesize some B-Vitamins.[14,15]

Oral Contraceptives and Hormone Replacement Therapy

Estrogen-containing drugs interrupt the conversion of tryptophan to niacin. In poorly nourished women signs of pellagra have been known to occur for this reason.[16,17]

Isoniazid

This medication indirectly decreases the amount of Niacin in the body and may, therefore, increase Niacin requirement.[18]

Anticonvulsants

Niacin inhibits the breakdown of certain anticonvulsants, namely primidone and carbamazepine, which could alter the dosing requirement for these medications. Beware any signs of drug toxicity if combined with Niacin supplementation.[19]

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Vitamin B6 - Pyridoxine, Pyridoxal and Pyridoxamine

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Introduction

Vitamin B_6 is involved in the formation of body proteins, red blood cells, anti-inflamatory prostaglandins, the synthesis of brain neurotransmitters and proper function of the immune system. It is required by more than 60 different enzymes.

Absorption and Metabolism

Vitamin B_6 is rapidly absorbed in the upper small intestine. After absorption, all three forms of Vitamin B_6 are converted to pyridoxal phosphate, the active coenzyme form. Although pyridoxal phosphate is found in all the tissues of the body, there is no real storage. It is excreted in the urine mainly as pyridoxic acid, along with small amounts of pyridoxal and pyridoxamine.

Functions

Unlike Vitamins B_1, B_2, B_3, biotin, and panthothenic acid, Vitamin B_6 does not participate directly in energy metabolism. Rather it is a coenzyme involved in protein metabolism, prostaglandin synthesis and immune modulation.
Protein and Amino Acid Metabolism
Transamination: e.g., conversion of alanine to pyruvate for energy production and gluconeogenesis.

Decarboxylation: in the synthesis of neurotransmitters (e.g., serotonin, norepinephrine, histamine (the vasodilator)): histadine conversion to histamine.

Transsulfuration: transfer of a sulfur group from one amino acid to form another (i.e., serine converted to cysteine).

Side-chain transfers: conversion of methionine to cysteine.

Hemoglobin synthesis
Conversion of tryptophan to niacin.
Formation of Prostaglandins series one and three.
Myelin sheath formation around nerve cells.
Immune system support.

Recommended Daily Allowance (RDA) Vitamin B_6

Group		Milligrams
Infants		
Under 6 months		0.3
6-12 months		0.6
Children		
	1-3 years	1.0
	4-6 years	1.1
	7-10 years	1.4
Young Adults and Adults		
Males	11-14 years	1.7
	15+ years	2.0
Females	11-14 years	1.5
	15+ years	1.6
Pregnancy		2.2
Lactation		2.1

Classic Vitamin B_6 Deficiency

Deficiency of Vitamin B_6 is characterized by:

1. Depression
2. Convulsions (especially in children)
3. Glucose Intolerance (B_6 is needed for glucose release from liver)
4. Nausea and vomiting
5. Anemia (microcytic)
6. Impaired nerve function, peripheral neuritis, altered mobility
7. Cracking of lips and tongue
8. Seborrhea or eczema

Vitamin B_6 Supplementation

Supplementation appears to be beneficial for a number of health concerns as Vitamin B_6 plays a vital role in the multiplication of all cells. It is, therefore, of critical importance to a healthy pregnancy, proper immune system function, mucous membranes, skin, and red blood cells. These tissues have a greater than average need for Vitamin B_6 due to the high replication rate of these cells.[1]

Lowers Homocysteine (Decreasing Heart Disease Risk)

Supplementation with folic acid and Vitamin B_{12}. Vitamin B_6 also helps to lower homocysteine levels by converting homocysteine to cystathionine; as a coenzyme for cystathionine B-synthase enzyme. A recent trial included 100 mg of Vitamin B_6 in patients with hyperhomocysteinemia (plus 500 mcg of folic acid) and demonstrated a successful lowering of blood homocysteine levels.[2]

Decreased Platelet Aggregation

Supplementation of 5 mgs per kg of body weight demonstrates a 41 percent to 48 percent reduction in platelet aggregation.[3,4] However, be aware that neurotoxicity can occur at intakes above 100-150 mg per day.

Reduces Inflammatory Conditions

Vitamin B_6 supplementation has been shown to be effective for carpal tunnel syndrome and premenstrual syndrome. Experimental evidence reveals that Vitamin B_6 favourably affects prostaglandin synthesis increasing anti-inflammatory prostaglandin 1 and 3 (PG1 and PG3), and helping to decrease pro-inflammatory PG2.

The main biochemical interventions appear to be increasing the activity of delta-6-desaturase enzyme, which increases the conversion of alpha-linolenic acid to EPA and DHA. EPA can be converted to PG3, exerting an anti-inflammatory effect.

EPA – eicosapentaenoic acid DHA – docosahexaenoic acid	>	[These are omega-3 fats commonly found in fish.]

Typical daily dosage to control inflammatory conditions ranges from 25-100 mg.[5-13] It seems plausible that Vitamin B_6 supplementation can be used to help control all inflammatory conditions mediated by prostaglandin synthesis.

Autism and Attention Deficit Hyperactivity Disorder

A number of clinical trials and experimental evidence suggests that Vitamin B_6 may be part of adjunctive treatment to help in these childhood conditions. Only about 20 percent of subjects may show moderate improvement and 10 percent more dramatic improvement with Vitamin B_6 supplementation. Vitamin B_6 is the coenzyme for brain decarboxylation enzymes, helping to synthesize dopamine, GABA, and serotonin which appear to be involved in these disorders. In this regard, Vitamin B_6 appears to work best in conjunction with magnesium supplementation. The usual dosage is 25-50 mg of Vitamin B_6 and 200 mg of magnesium per day.[14-27]

Depression (secondary to birth control pill and hormone replacement therapy)

Vitamin B_6 levels are often low in females taking birth control pills or Premarin. Supplementation with 50-100 mg of Vitamin B_6 per day has been shown to help reverse the depression that may result from taking these drugs.[28-31]

Asthma

Double-blind clinical studies show that some patients with asthma benefit from Vitamin B_6 supplementation (50 mg twice daily) to correct defects in tryptophan and serotonin metabolism. Also, the asthmatic drug theophylline decreases pyridoxal-5-phosphate levels, and B_6 supplementation reduces theophylline-induced side effects (headache, nausea, irritability, sleep disorders).[32-35]

Childhood Seizures, Tardive Dyskinesia and Epilepsy

A number of clinical trials reveal that Vitamin B_6 supplementation at 50-100 mg per day may be helpful for these conditions. Be aware that doses over 80 mg may interfere with anticonvulsant therapy in epileptics.[36-39]

Diabetic Neuropathy

Vitamin B_6 supplementation has been shown to improve diabetic neuropathy and inhibit the glycosylation of proteins, a key prognostic indicator of diabetic control and risk of complications.[40,41] 50-100 mg per day may be useful in this regard.

Kidney Stones

Vitamin B_6 supplementation has been shown to help prevent recurrence of calcium oxalate kidney stones. This effect is best by combining B_6 and magnesium supplementation. 50-100 mg of Vitamin B_6 (up to 300 mg) and 200-300 mg magnesium.[42,43]

Vitamin B6 Toxicity

Neurotoxicity from excess Vitamin B_6 intake can occur at doses as low as 100-150 mg per day, take over many months. Signs and symptoms of neurotoxicity include:

Tingling sensation in feet
Loss of muscle coordination
Degeneration of nerve tissue

Therefore, it is best to limit Vitamin B_6 supplementation to 50 mg. In some instances it can be taken up to 100 mg per day in divided doses.[44-47]

Drug-Nutrient Interactions

1. Levodopa

Vitamin B_6 may increase the breakdown of levodopa, possibly altering the drug's effectiveness in Parkinson's patients. However, the use of a drug combining levodopa with carbidopa (Sinemet) is reported to avoid this potential problem.[48]

2. The following drugs are reported to cause Vitamin B_6 depletion:

Antibiotics-decrease B-vitamin synthesis by bacterial flora.[49,50]

Oral contraceptives and Hormone Replacement Therapy (estrogen-containing drugs).[51]

Hydralazine.[52,53]

Loop Diuretics - cause increased urinary loss of Vitamin B_6[54]

Isoniazid[55,56,57]

Penicillamine[58,59,60]

Phenelzine[61]

Theophylline - decrease the active form of Vitamin B_6[62]

Pregnancy and Lactation

During pregnancy and lactation, the only supplements that are considered safe include standard prenatal vitamin and mineral supplements. All other supplements or dose alterations may pose a threat to the developing fetus and there is generally insufficient evidence at this time to determine an absolute level of safety for most dietary supplements other than a prenatal supplement. Any supplementation practices beyond a prenatal supplement should involve the cooperation of the attending physician (i.e., magnesium and the treatment of preeclampsia.)

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Vitamin B_{12} - Cobalamin

Introduction

Cobalamin is the generic name for Vitamin B_{12} because of the presence of cobalt. Several of the different Cobalamin compounds exhibit Vitamin B_{12} activity. Of these compounds, cyanocobalamin and hydroxycobalamin are the most active forms. Cyanocobalamin is the most stable form and therefore, the form in which the vitamin is produced commercially from bacterial fermentation. Vitamin B_{12} is best known for its role in preventing pernicious anemia.

Absorption and Metabolism

Cobalamin is poorly absorbed from the intestinal tract unless the intrinsic factor in gastric secretion is present. Intrinsic factor binds with Vitamin B_{12} forming a complex that binds with a specific receptor in the membrane of the ileum allowing its absorption into the blood stream to occur. Intrinsic factor is a mucoprotein enzyme made in the stomach. Vitamin B_{12} injections are often given to prevent the development of pernicious anemia and other symptoms of Vitamin B_{12} deficiency in certain individuals who are unable to synthesize intrinsic factor. In the absence of intrinsic factor only 1-3 percent of Vitamin B_{12} can be absorbed via simple diffusion. Normal people absorb up to 30 percent of a test dose of Vitamin B_{12}. However, in individuals with low intakes, absorption may increase up to 70 percent.

There is an enteroheptatic circulation of B_{12} that recycles it from bile and other intestinal secretions to the bloodstream from the intestinal tract. This is the reason why Vitamin B_{12} deficiency takes so long to develop in humans, as a result of insufficient intake or age-related malabsorption.

Functions

In conjunction with folic acid, Vitamin B_{12} enables each cell in the body to recycle homocysteine to methionine by providing an all-important methyl group. From methionine, the body easily makes S-adenosyl methionine by adding an adenosyl ring from ATP. Once formed, S-adenosyl methionine can transfer its methyl group to permit the synthesis of thymine nucleotides of DNA, neurotransmitters in the brain, creatine in the liver and other crucial functions, including a direct effect on detoxification reactions in the liver. A deficiency of either folic acid or Vitamin B_{12} results in megaloblastosis, or the development of red blood cells that are enlarged because normal cell division has not taken place. Vitamin B_{12} is also required by nerve cells as a stabilizer of glutathione, which is needed for carbohydrate metabolism. An absence of B_{12} then hinders the energy metabolism of nerve cells. As well, in its methyl-form Vitamin B_{12} is necessary for the formation and maintenance of myelin, the protective coating sheathing the axons of nerve cells. The B-vitamin biotin assists B_{12} in this role.

Recommended Daily Allowance (Vitamin B_{12})

Group	Micrograms
Under 6 months	0.3
6-12 months	0.5
1-3 years	0.7
4-6 years	1.0
7-10 years	1.4
11+ years	2.0
Pregnant females	2.2
Lactating females	2.1

Vitamin B12 Deficiency

Unlike other water-soluble nutrients, Vitamin B_{12} is stored in the liver, kidney, and other body tissues. As a result, signs and symptoms of Vitamin B_{12} deficiency may not show themselves until 5 to 6 years of poor dietary intake or inadequate secretion of intrinsic factor. Lack of intrinsic factor occurs from an inborn error of metabolism and as a result of aging.

Pernicious Anemia

Although hereditary, it rarely manifests itself before age 35. Classic signs include megaloblastic anemia. The anemia may be severe, with a hematocrit as low as 10-15%. The megaloblastic state also produces changes in mucosal cells, leading to glossitis, as well as other vague GI disturbances such as anorexia and diarrhea. Vitamin B_{12} deficiency also leads to a complex neurological syndrome, including peripheral paresthesia followed by poor balance due to involvement of the posterior column. In severe cases, cerebral function may be altered (e.g. dementia, other neuropsychiatric changes).

Of note is the fact that neurological involvement precedes the anemia. Therefore, in Vitamin B_{12} deficiency the nervous system and brain are affected first. Note that a high intake of folic acid may mask a Vitamin B_{12} deficiency because it prevents the changes in red blood cells, but does not counteract the deficiency in the brain and nervous system.[1]

Supplementation Studies

Impaired Mental Function in the Elderly (Senility)

Impaired mental function in the elderly can be a result of reversible nutritional deficiencies. Several clinical trials have noted improvement in cognitive function in older persons when supplemented with Vitamin B_{12} and/or folic acid. Supplements appear to be indicated in cases of high homocysteine and/or low blood levels of Cobalamin. A dosage of Vitamin B_{12} is typically 100-500 mcg to correct the deficiency, then a maintenance dose of 25-75 mcg per day.[2-10]

Diabetic Neuropathy

Some success has been realized using Vitamin B_{12} supplementation in diabetic neuropathy. Injections are most common, but oral intake of 1.5 to 2.0 mg per day may produce the same results.[11-14]

Multiple Sclerosis

Supplementing with methylocobalamin at 60 mg per day was shown to improve both visual and brainstem auditory-evoked potentials by nearly 30 percent. Motor function did not improve, indicating a benefit to afferent not efferent nerve pathways.[15]

Low Sperm Count

In men with a low sperm count (<20 million per ml or a motility rate of less than 50 percent), two studies have demonstrated improvement (achieved a total count of 100,000 million per ml) with daily doses of 1,000 mcg and 6,000 mcg of Vitamin B_{12} daily (taken orally).[16,17]

Vitamin B_{12} Toxicity

Vitamin B_{12} is not known to have any toxic effects at any reasonable intake level.[1]

Drug-Nutrient Interactions

The following drugs are reported to cause depletion of Vitamin B_{12}:
Oral contraceptives[18]

Antibiotics decrease the synthesis of various B-vitamins by the bacterial flora of the large intestine.[19,20]

Antiviral drugs (didanosine, lamivudine, stavudine, salcitabine, zidovudine).[21]

Biguanides (e.g. metformin) may reduce Vitamin B_{12} absorption in approximately 30% of patients.[22]

Bile Sequestrants (cholestyramine, colestipol) decrease VitaminB_{12} absorption.[23]

Clofibrate and possible other fibrate drugs decrease Vitamin B_{12} absorption.[24]

Colchicine is reported to reduce Vitamin B_{12} absorption.[25]

H_2 Receptor Antagonists (cimetidine, famotidine, mizatidine, ranitidine) these drugs reduce VitaminB_{12} absorption by decreasing stomach acidity.[26]

Phenytoin (anti-consulsant) may decrease VitaminB_{12} absorption.[27]

Proton Pump Inhibitors may reduce Vitamin B_{12} absorption by decreasing stomach acidity (e.g. lansoprazole, omeprazole, rabeprazole, pantoprazole).[28]

Time-released potassium chloride, these medications can reduce stomach acidity and may decrease Vitamin B_{12} absorption as a result.[29]

Pregnancy and Lactation

1. *During pregnancy and lactation, the only supplements that are considered safe include standard prenatal vitamin and mineral supplements. All other supplements or dose alterations may pose a threat to the developing fetus and there is generally insufficient evidence at this time to determine an absolute level of safety for most dietary supplements other than a prenatal supplement. Any supplementation practices beyond a prenatal supplement should involve the cooperation of the attending physician (e.g., magnesium and the treatment of preeclampsia.)*

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Folic Acid

Introduction

Folic Acid is a water-soluble B-vitamin that is comprised of pteridine, para-aminobenzoic acid (PABA) conjugated with one, three or seven molecules of glutamic acid. Some of the glutamic acid molecules must be split off to form an unconjugated Folic Acid molecule, pteroylmonoglutamic acid (PGA), which is the active form referred to as Folic Acid. Vitamin B_{12} is required to convert Folic Acid into its active form. Because Folic Acid was first discovered in spinach leaves, it was called Folic Acid from the Latin "folium" leaf.

Absorption and Metabolism

Folic Acid is well absorbed from the intestinal tract. In the presence of Nicotinamide Adenine Dinucleotide (NAD), Folic Acid is reduced to tetrahydrofolic acid in the body. The liver contains half the body stores of Folic Acid.

Functions

In conjunction with Vitamin B_{12}, Folic Acid enables each cell in the body to recycle homocysteine back to methionine by providing an all-important methyl group. From methionine the body easily makes S-adenosyl methionine by adding an adenosyl ring from Adenosine Triphosphate (ATP). Once formed, S-adenosyl methionine can transfer its methyl group to permit the synthesis of thymine nucleotides of DNA, neurotransmitters in the brain, creatine in the liver and other crucial functions, including a direct effect on detoxification reactions in the liver. A deficiency of either Folic Acid or Vitamin B_{12} results in megaloblastosis, or the development of red blood cells that are enlarged because normal cell division has not taken place.[1]

As a major dietary source of a transferable methyl group, Folic Acid is a vital nutrient for DNA synthesis and hence, the prevention of neural tube defects (e.g., spina bifida, anencephaly) and hypomethylation of DNA, which is linked to increased cancer risk.[2,3]

Because it helps to recycle homocysteine to methionine it is also important in the prevention of atherosclerosis, due to its ability to contain the build up on homocysteine. When elevated levels of homocysteine occur in body cells, it diffuses out of the cells to enter the bloodstream. In the bloodstream homocysteine oxidizes LDL-cholesterol, promotes vasoconstriction, coagulation of platelets, thereby accelerating the atherosclerotic process leading to heart attack, stroke and peripheral vascular disease.[4,5]

Folic Acid is vital for the synthesis of red blood cells, hence the onset of megaloblastic anemia in folate deficiency.

Recommended Dietary Allowance (Folic Acid)

Group	Micrograms
Infants:	
Under 6 months	25
6-12 months	35
Children:	
1-3 years	50
4-6 years	75
7-10 years	100
Young Adults and Adult	
Males 11-14 years	150
15+ years	200
Females 11-14 years	150
15+ years	180
Pregnancy	400
Lactation	280[1]

Supplementation Studies

Prevention of Neural Tube Defects

If all women of childbearing age ingested a minimum of 400 mcgs of Folic Acid from a combination of food and supplementation, there would be a 48 percent reduction in the incidence of neural tube defects. Presently, the average ingestion of Folic Acid is only 180 mcg per day from food.[2]

Heart Disease

Elevated homocysteine is considered to account for approximately 10 percent of the risk for coronary artery disease.[4] Supplementation studies with Folic Acid have been shown to reduce elevated homocysteine levels into a safer range (<10 micromoles per litre, or µmol/L). Folic Acid supplementation of 200 mcg reduces homocysteine by approximately 4 µmol/L. A 5 µmol/L homocysteine increment elevates coronary artery disease risk by as much as a cholesterol elevation of 0.5 µmol/L (20 mg/dL). Supplementation studies to lower homocysteine have used 1 to 2.5 mg of Folic Acid daily. Note that Vitamin B_6 and Vitamin B_{12} are also important to homocysteine metabolism. These vitamins work synergistically with Folic Acid to lower and regulate homocysteine levels.[4-8]

Cervical Dysplasia

In clinical studies Folic Acid supplementation (10 mg per day) has been shown to reverse early and moderate stage cervical dysplasia as demonstrated by pap smear testing. Success rates vary from 20 to 100 percent. Folic Acid appears to improve the integrity (chromosomal linkages) of cervical DNA, making it less resistant to the effect of the human papilloma virus (HPV). The HPV is known to cause cervical dysplasia.[9,10,11]

The B-vitamin Folic Acid is critical to synthesis of normal DNA as cells divide from one generation to the next. Cells that line the cervix replace themselves every 7-14 days and, therefore, the cells must continuously form DNA as part of their genetic structure. Previous studies have demonstrated that poor Folic Acid status can lead to DNA abnormalities

with subsequent development of cervical dysplasia or megaloblastic features of cervical cells (large abnormal cell appearance).

Oral contraceptives are known to increase the rate of cell division of cervical cells, hence, escalating the need for adequate Folic Acid intake. Studies by Whitehead et al. and Butterworth et al. demonstrated that Folic Acid supplementation could reverse cervical megaloblastic charges and cervical dysplasia, respectively, in patients using oral contraceptives. In fact, oral contraceptive use is a known risk factor for cervical dysplasia, primarily due to its effect on speeding up cell division rates.

In the study by Butterworth et al., patients with mild and moderate degrees of cervical dysplasia showed reversal of their condition over a 3-month trial period with Folic Acid supplementation.

In both studies the authors noted a statistically lower mean red blood cell Folic Acid concentration in oral contraceptive users compared with non-users, which was particularly marked in patients with cervical dysplasia. Red blood cell Folic Acid levels are considered a good indicator of Folic Acid status.

Other population studies (epidemiologic) consistently support the hypothesis that Folic Acid plays a protective role in the prevention of cervical dysplasia.

Unfortunately, up to 88 percent of the population consumes less than 400 mcg per day of Folic Acid. This is the level that women should ingest to reduce the risk of spinal birth defects in their offspring, and may help defend against cervical dysplasia.[12]

Depression in the Elderly

Correction of an underlying Folic Acid deficiency has demonstrated significant reversal of mental and psychological symptoms in some patients, especially elderly patients suffering from impaired mental function. Folic Acid is required to synthesize S-adenosyl-methionine and tetrahydrobioptein (BH_4). These substances participate as coenzymes in the production of serotonin, thus exerting a mild antidepressant effect. To correct a folate deficiency where psychological symptoms are present, a daily dose of 10 mg is used until the deficiency state is corrected (see Vitamin B_{12} for more details).[13-18]

Interactions

Folic Acid supplementation should always include Vitamin B_{12} supplementation (400-1,000 mcg Folic Acid) because Folic Acid supplementation can mask an underlying Vitamin B_{12} deficiency, until serious neurological signs and symptoms of B_{12} deficiency manifest themselves.[1]

Folic AcicToxicity

Folic Acid is well tolerated, even at high daily dosages used to treat cervical dysplasia (e.g. 5-10 mg). However, high dosages can cause nausea, loss of appetite and gastro-intestinal-upset. It may also increase seizure activity in epileptics.

Drug-Nutrient Interactions

Antacids (containing aluminum/magnesium): These drugs reduce stomach acid and consequently impair Folic Acid absorption[19]
Bile Acid Sequestrants (cholestyramine, colestipol): These drugs decrease Folic Acid absorption.[20]
H_2 Receptor Antagonists (cimetidine, famotidine, nizatidine, ranitidine): These drugs decrease stomach acid and thereby also decrease Folic Acid absorption[21]

Potassium Sparing Diuretics (triamterene, HCT21 triamterine): These drugs inhibit Folic Acid absorption in animal studies.[22,23]
Alcohol: Excessive alcohol intake depletes Folic Acid status.[24]
Anticonvulsants (barbituates, fosphenytoin, phenytoin, carbamazepine, primidone): These drugs are reported to deplete Folic Acid levels. However, high dose Folic Acid supplementation may counteract the drugs' effectiveness.[25-29]
Salicytates: These drugs increase urinary loss of Folic Acid (eg. Aspirin, diflunisal, salsalate).[30,31]
Corticosteroid Drugs (prednisone): These drugs are reported to decrease blood levels Folic Acid.[32]
Non Steroidal Anti-inflammatory Drugs (NSAIDs): Animal studies reveal that these drugs interrupt the use of Folic Acid in the body.[33]
Oral Contraceptives: These drugs promote Folic Acid depletion.[34,35]
Metformin: This drug is reported to cause depletion of Folic Acid.[36]
Methotrexate: This cancer drug is designed to interrupt the use of Folic Acid by cancer cells to block their DNA syntheses. Do not supplement with Folic Acid if patient is taking methotrexate for cancer treatment.[37,38] Conversely, patients taking methotrexate to treat rheumatoid diseases are usually instructed to take Folic Acid.
Trimethoprim Containing antibiotics: These drugs promote Folic Acid depletion.[39]
Sulfasalazine: Animal studies suggest that this drug interrupts the use of Folic Acid.[40]

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Pantothenic Acid

Introduction

Its name "Pantothenic Acid" reflects its widespread (pan-) distribution in plant and animal foods. All foods contain this B-vitamin, thus an overt pantothenic acid deficiency is rare, unless induced by starvation or by consuming a purified diet in combination with pantothenic acid antagonists for experimental reasons.

Absorption and Metabolism

Pantothenic acid is absorbed in the small intestine (passive diffusion is considered to be the mechanism). In the body tissues, the vitamin is converted to its important coenzyme form, Coenzyme A. Pantothenic acid is also a component of acyl-carrier protein (ACP), used in fatty acid synthesis.

Functions

As a component of coenzyme A, the subsequent formation of Acetyl CoA is central to the production of ATP in the Kreb's cycle, fatty acid synthesis, cholesterol synthesis, ketone formation and the production of the neurotransmitter acetylcholine.

Recommended Dietary Allowance (Pantothenic Acid)

Group	Milligrams
Under 6 months	2
6-12 months	3
1-6 years	3-4
7-10 years	4-5
11+ years	4-7

Clinical Deficiency

Experimentally-induced deficiency of pantothenic acid results in insomnia, fatigue, irritability, numbness and tingling of the hands and feet, muscle cramps, and impaired production of antibodies. Administration of pantothenic acid eliminates all of these symptoms.

Supplementation Studies

Pantothenic acid has been used successfully to treat neurologic symptoms in patients who have received streptomycin.

Pantothenic acid is sometimes used to stimulate the gastrointestinal tract following surgery.[1]

Cholesterol and Triglyceride Lowering

Pantethine is a more active form of pantothenic acid (and more expensive) has been shown to lower cholesterol and triglyceride levels. Preliminary clinical trails demonstrate that taking 300 mg of pantethine, three times per day (900 mg dose) can reduce serum triglyceride levels by 32 per cent and total cholesterol levels by 19 per cent. In contrast to many cholesterol-lowering drugs it exhibits very little toxicity and appears to be safe for this application. Pantethine

acts by inhibiting cholesterol synthesis and accelerating the utilization of fat as an energy source.[2,3] Several studies have shown that pantethine produces impressive lipid-lowering effects without side effects in diabetics.[4,5,6]

Author's Note: 900 mg of pantethine is a very high dose. Long term studies are likely needed to establish the true safety of this B-vitamin like substance if doses in this range are to be used for lowering lipids. Other natural agents can be used to lower lipids, such as gugulipid, policosanol, soy, garlic extract, soluble fibre, reduced intake of saturated fat, psyllium and flax seed powder. All of these have established safety for this application. Pantethine should still be considered experimental until further studies evaluating its safety are completed.

Adverse Side Effects and Toxicity of Pantothenic Acid

No toxic effects are known other than at doses of 10 to 20 grams, which may cause diarrhea.

Drug-Nutrient Interactions

Salicylates

ASA and salicylate-containing drugs are reported to cause a decrease in pantothenic acid levels in the body.[7]

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Biotin

Introduction

Before its final identification as Biotin, this B-Vitamin was known as Bios IIb and Vitamin H by researchers in the first half of the twentieth century. In 1942, its chemical structure was identified, and with its synthesis the following year, Biotin was officially added to the roster of water-soluble vitamins.

Absorption and Metabolism

Significant amounts of Biotin are synthesized by bacteria in the large intestine. Nutritional Biotin is well absorbed and occurs in all the cells of the body, although in minute amounts.

Within body cells it is bound to protein, in which it serves its coenzymatic functions.

Excess Biotin is excreted in the urine. Excretion of three to six times the amount of Biotin ingested has been demonstrated; emphasizing that bacterial synthesis contributes large quantities to the body's available supply. As such, the use of antibiotics is known to decrease the amounts of Biotin available for absorption from the intestine. Particularly oxytetracycline and the sulfonamides have been shown to produce signs and symptoms of secondary Biotin deficiency with long-term use.

The egg white protein known as avidin is known to complex with Biotin in the gut and prevent its absorption. By cooking the egg the avidin is denatured, eliminating the risk of impaired Biotin absorption. In this instance the risk of Biotin deficiency would require that a person depend solely upon raw eggs as their source of dietary protein. According to one estimate, the avidin content of more than 20 raw eggs per day for several weeks would be required to create a Biotin deficiency.

Functions

Biotin primarily serves a coenzyme role:

1. Carbon dioxide carrier in CO_2-fixation reactions (carboxylation). These reactions are important for fatty acid synthesis and oxidation.
2. Deamination of certain amino acids (notably threonine, aspartic acid, serine).

Recommended Dietary Allowance (Biotin)

Group		Micrograms
Infants:	Under 6 months	10
	6-12 months	15
Children:	1-10 years	30
	11+ years	30-300

Clinical Deficiency

Overt deficiency is rare, but appears as:
Greyish, dry, scaly skin (especially, nose and mouth)
Loss of Appetite
Lassitude
Muscle Pain
Nausea
Extremity Paresthesia
Depression
Hair Loss

As a rule, in adults with seborrheic dermatitis treatment with Biotin alone is usually of no value. More effective treatment includes the use of all the B-vitamins required for fatty acid synthesis (Biotin, Vitamin B6, pantothenic acid, niacin, thiamin).[1]

Biotin Supplementation Studies (above RDA)

Brittle nails

Recent human studies have shown that Biotin supplementation (2,500 mcgs per day) can produce a 25 percent increase in the thickness of the nail plate in patients diagnosed with brittle nails of unknown cause, with up to 91 percent of patients taking this dosage experiencing improvement.[2] This research is an extension of animal studies, which demonstrated that Biotin increases the strength and hardness of hooves in pigs and horses.

Infant Seborrheic Dermatitis

Biotin supplementation given to the infant or the breast-feeding mother has been shown to be effective in treatment of "cradle cap" (Seborrheic dermatitis in infants 2-12 weeks of age).[3,4] (3,000 mcgs, 2X daily to mother or 100-300 mcg to infant)

Increased Insulin Sensitivity In Diabetes

Biotin supplementation enhances insulin sensitivity and increases the activity of the enzyme glucokinase in glucose metabolism. In one study, 16 mgs of Biotin per day resulted in significant lowering of fasting blood glucose in type I diabetics).[5] The same has been shown in type II diabetics with a dosage of 9 mgs per day.[6]

Diabetic Neuropathy

High dose Biotin has been shown to improve severe diabetic nerve damage. 8 mgs, twice per day is the usual dosage.[7]

Biotin Toxicity

Biotin is extremely safe, and there are no reports of side effects with Biotin supplementation.[8]

Drug-Nutrient Interaction

1. Antibiotics

Various types of antibiotics kill off the Bifidobacterium in the large intestine that synthesize Biotin as well as other B-vitamins. Antibiotics implicated in this regard include:

- Aminoglycosides
- Cephalosporins
- Flurosoquinolones
- Macrolides
- Penacillins
- Sulfonamides
- Tetracyclin
- Trimethoprim[9]

2. Anticonvulsants

Anticonvulsants are reported to deplete Biotin in the body (barbiturates, primidone, carbamazepine, phenytoin).[10,11,12]

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Vitamin C - Ascorbic Acid

Introduction

The name Ascorbic Acid is derived from the Latin *ascorbutus* meaning "without scurvy". In the winter of 1534, local Canadian Indians provided Jacques Cartier with the cure for scurvy, which had claimed twenty-five of his 110 men, with more than fifty in critical condition. The cure included a tea containing evergreen foliage from the Northern white cedar.

Ascorbic Acid itself was not identified as the anti-scorbutic agent until the early 1930s. It was first synthesized in 1933.

Absorption and Metabolism

Vitamin C is readily absorbed through the mucosa of the intestine. Humans store a total of 1,500 mg with moderate reserves in the liver and spleen, and high concentrations in the adrenal glands where it may be involved in the synthesis of adrenal steroids. Serum and tissue levels are in equilibrium; therefore, white blood cell levels of Vitamin C reflect Vitamin C stores in general.

The body excretes Vitamin C as Ascorbic Acid and as the metabolite oxalic acid in the urine. Thus, high Vitamin C intakes (above 750 mg) may precipitate the formation of calcium-oxalate kidney stones, in susceptible individuals.

Functions

1. **Cartilage Formation**

   Ascorbic Acid is necessary for the transformation of the amino acids proline and lysine into hydroxyproline, which provide the tertiary structure to collagen. This provides stability to collagen, a major component of all connective tissues in the body - skin, bones, teeth, muscle, tendon, cornea, etc. Thus, a Vitamin C deficiency manifests itself as swollen limbs, blotched and haemorrhaging gums and skin, loss of teeth, severe weakness, followed by death if untreated (scurvy).

   Vitamin C is required for wound healing. Therapeutic doses are used in the treatment of post-surgical patients and burn victims, primarily to support collagen synthesis.

2. **Neurotransmitter Synthesis**

   Vitamin C is required for the synthesis of norepinephrine from dopamine.

3. **Iron Absorption**

   The presence of Vitamin C enhances the absorption of iron from the intestinal tract to the bloodstream.[1]

4. **Antioxidant**

   Vitamin C functions as an antioxidant in aqueous (water) environments in the body, both outside and inside human cells.[1] It also regenerates oxidized Vitamin E back to its antioxidant state, thereby potentiating the free radical quenching capability of Vitamin E.[2]

5. **Immune Function**

   Vitamin C is required to maintain optimal function of the immune system.[3]

Recommended Dietary Allowance (Vitamin C)[1]

Group	Milligrams
Under 6 months	30
6-12 months	35
1-3 yrs	40
4-10 yrs	45
11-14 yrs	50
15+ yrs	60
Pregnant females	70
Lactating females	95

Vitamin C Deficiency

Scurvy:

- Lassitude and general weakness
- Swollen joints
- Aching bones
- Spongy and bleeding gums
- Delayed wound healing
- Muscle cramps
- Dry, scaly skin

Signs of scurvy appear once the body pool of Vitamin C drops below 300 mg. Signs and symptoms of scurvy disappear when the body pool is restored to this level. Groups most at risk in North America include alcoholics and the elderly. Interestingly, Eskimos in the Arctic are able to derive Vitamin C from eating food frozen, raw, or only partially cooked although consuming a diet of almost no plant-based foods. Cooking destroys Vitamin C as it is the least stable of all vitamins (becomes readily oxidized when heated or exposed to light, air or an alkaline solution).[1]

Supplementation Studies

Cancer prevention

A significant number of studies link higher intakes of Vitamin C with the prevention of cancer. Reports are most consistent for lung cancer, stomach, esophageal, oral, cervical, colon and pancreatic cancers.[4] The following are mechanisms through which Vitamin C has been shown to modify cancer risk:

Antioxidant Function: as previously discussed, Vitamin C is a water soluble antioxidant, which has been shown to help contain oxidative stress and other free radical insults that are capable of causing mutations to the cell's DNA, potentially leading to cancer.[1,4]

Nitrosation Inhibitor: Vitamin C is known to block the formation of nitrosamines in the intestinal tract. Certain nitrosamines are known to be cancer-causing agents (carcinogens). Nitrosamines are formed by nitrosation reactions that combine nitrites (found in many processed foods and alcoholic beverages) with derivatives of dietary proteins, known as secondary amines. In test studies using nitrate loads, doses of approximately 1,000 mg per day of Vitamin C have been shown to block 85-100 percent of nitrosamine formation in human subjects. It appears best to take Vitamin C with food (500 mg, twice daily) in divided doses to get the best possible effect in blocking nitrosation reactions.[5,6]

Immune Function

Vitamin C supplementation has been shown to boost parameters of immune function in normal volunteers and in elderly subjects. A daily dosage of only 120 mg per day has been shown to boost white blood cell counts back to more youthful levels in older people (average age 76). However, a daily dosage of 500-1,000 mg appears to further strengthen the immune system and reduce the severity and duration of the common cold,[7-10] In patients exposed to toxic chemicals a daily dosage of 60 mg per kilogram of body weight (about 4,000 mg per day) has been shown to greatly enhance natural killer cell function (up to 10-fold) and restore B and T cell function.[11]

Asthma

Asthmatics may have a higher requirement for Vitamin C than do members of the general population. At least eleven clinical studies of Vitamin C supplementation have been performed with asthmatic patients. Seven of these studies showed significant improvements in respiratory measures and asthma symptoms using 1,000-2,000 mg of Vitamin C supplementation per day. At this level of intake Vitamin C has been shown to have an anti-histamine effect and it helps prevent lung damage from nitrogen oxide, a common dangerous element in air pollution and cigarette smoke.[29,30]

Cancer Treatment

As part of an antioxidant and nutritional support cocktail, a daily dosage of 2,850 mg of Vitamin C has been shown to help stop the further spread of breast cancer in a trial of 32 breast cancer patients with axillary lymph node involvement. Researchers having success in this area tend to use high doses of supplementation of various nutrients concurrently (e.g. Vitamin E-2,500 I.U., selenium-387 mg, Coenzyme Q10-350 mg., Beta-carotene-50,000-150,000 I.U.).[12] There is presently sound scientific evidence to consider antioxidant supplementation during and/or following chemotherapy according to a number of published peer-reviewed articles and investigative studies in cancer patients.[13,14]

Cataracts

Individuals with higher intakes of Vitamins C and E, selenium and carotenes have a much lower risk for developing cataracts and macular degeneration than do individuals with lower intakes. Vitamin C supplementation at 1,000 mg per day has been shown to significantly reduce the incidence of cataracts, halt cataract progression and, in some cases, improve vision.[15,16]

Diabetes Mellitus

Insulin is required to help transport Vitamin C into the cells of the body. Thus many diabetics have a higher requirement for Vitamin C than do nondiabetics.[17] In a 90 day study type II diabetics who were given 600 mg of magnesium and 2,000 mg of Vitamin C per day showed improved glycemic control, fasting blood glucose and a lowering of blood cholesterol and triglycerides.[18] Daily doses of 100 and 600 mg per day of Vitamin C has also been shown to reduce levels of sorbitol in diabetics. Sorbitol is a primary contributor of cataract development in diabetics.[19,20]

Furthermore, Vitamin C supplementation in diabetics may help to reduce capillary fragility, which also contributes to vascular complications in the population. Vitamin C has been shown to improve endothelium-dependent vasodilation in patients with type I diabetes, helping to improve peripheral circulation.[21]

As well, a daily dosage of 1,000-3,000 mg per day has been shown to reduce blood levels of glycosylated proteins (e.g. albumin) by an average of 33 percent in diabetic subjects. This is a key marker in diabetes prognosis, with increased glycosylated proteins hastening the damage to the eye, kidneys, blood vessels and other organs.[22,23]

Male Fertility

Vitamin C appears to play an important role in protecting the sperm's genetic material (DNA) from damage and mutations. Low sperm counts are common in smokers, and Vitamin C supplementation has been shown to improve sperm quality and integrity in smokers in a dose-dependent fashion (using 0, 200 or 1,000 mg. per day).[24]

In infertile men who were non-smokers, Vitamin C supplementation has been shown to increase sperm counts by 140 percent within one week of taking 1,000 mg per day. Supplementation using 200-1,000 mg per day has also been shown to reduce sperm agglutination (agglutination increases the likelihood of infertility).[25]

Bed Sores

Higher intake levels of Vitamin C are associated with a lower frequency of bed sores in bed-ridden patients. Vitamin C supplementation has also been shown to enhance the healing of bed or pressure sores in a double-blind study.[26,27]

Aerobic Exercise Oxidative Stress

Oxidative stress causing free radical attack has been shown to be higher in exercising subjects not taking Vitamin C supplements on a regular basis.[28]

Dosage Ranges

Cancer Prevention and Nitrosamine Containment: studies suggest that 120-1,000 mg per day may be prudent.[4,5,6]
Immune System Function in Aging: 500-1,000 mg per day may return immune function a more youthful level of function.[7-11]
Asthma: 1,000-2,000 mg per day.[29,30]
Cataract: 500-1,000 mg per day.[16]
Diabetes mellitus: 1,000-3,000 mg per day.[17-22]
Male Infertility: 200-1,000 mg per day.[24,25]
Bed Sores: 500-1,000 mg per day.[27]

Vitamin C Toxicity and Side Effects

Vitamin C is very non-toxic and is readily excreted due to the body's inability to store appreciable amounts.

In certain people, Vitamin C supplementation can increase risk of kidney stones (calcium-oxalate) and exacerbate gouty arthritis. Patients with a previous history of kidney stones should limit their intake of Vitamin C to 750 mg or less. Patients with gout should not exceed a daily dose of 500 mg.

Rebound scurvy can develop in newborns whose mothers ingest mega doses of Vitamin C during pregnancy. Once the fetal metabolic system has adapted to the higher amounts by removing the excess Vitamin C more rapidly than normal, even the normal amounts ingested by the newborn are removed at the accelerated rate, depressing serum and tissue levels.[1]

Contra-indications

1. Kidney Stones (calcium-oxalate): Vitamin C intake should not exceed 750 mg per day from supplementation.
2. Gout: Vitamin C intake should not exceed 500 mg per day from supplementation.[1]

Drug-Nutrient Interactions

Vitamin C depletion can result from the administration of:

1. Adrenal steroids (e.g. coricorteroid drugs which decrease Vitamin C uptake by cells.)[31,32]
2. Salicylates – increase urinary loss of Vitamin C.[31,33,34]
3. Sulfonamides[31]
4. Tetracycline[31,35]
5. Cigarette smoking[31]
6. Oral Contraceptives[31,36,37]
7. Loop Diuretics: increase urinary loss of Vitamin C (e.g. furosemide, Bumetanide, ethacrynic acid, torsemide).[38]

N.B. Large amounts of Vitamin C intake can falsify urine tests in diabetics, disrupting the monitoring process for desirable insulin requirements.[31]

High doses of Vitamin C may decrease the absorption of copper.[39,40]

Pregnancy and Lactation

1. During pregnancy and lactation, the only supplements that are considered safe include standard prenatal vitamin and mineral supplements. All other supplements or dose alterations may pose a threat to the developing fetus and there is generally insufficient evidence at this time to determine an absolute level of safety for most dietary supplements other than a prenatal supplement. Any supplementation practices beyond a prenatal supplement should involve the cooperation of the attending physician (e.g., magnesium and the treatment of preeclampsia.)

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Vitamin D

Introduction

Since the Middle Ages, cod liver oil has been used to prevent and treat rickets. In 1930, Vitamin D was isolated and shown to be the fat-soluble compound in cod liver oil that was effective against rickets.[1]

In recent years, Vitamin D receptors have been discovered on tissues other than bone, and Vitamin D is now emerging as an important nutrient that may help reduce risk of colon, breast and prostate cancer due primarily to its effects on cellular differentiation and its anti-proliferative properties. Vitamin D may also help to reduce the risk of multiple sclerosis.[2]

Absorption and Metabolism

Vitamin D is a fat-soluble vitamin and is absorbed from the intestinal tract by means of chylomicrons (like Vitamins A and E), and is transported to the liver where it is stored. Vitamin D can also be acquired by exposure to direct sunlight (not through a window pane). Sunlight converts dehydrocholesterol to cholecalciferol (D_3) under the skin. Cholecalciferol then circulates to the liver, where like dietary Vitamin D, it can be converted to 25-hydroxycholecalciferol, which is five times more potent than cholecalciferol.

25-hydroxycholecalciferol circulates to the kidney where via further enzymatic hydroxylation it can be converted to 1, 25 dihydroxycholecalciferol, which is ten times more potent than cholecalciferol.[1,3] This form of Vitamin D (1, 25-dihydroxyvitamin D) is also known as calcitriol.

With aging, the body is less able to convert 25 hydroxycholecalciferol to 1,25 dihydroxycholecalciferol due to decreased activity of the kidney hydroxylase enzyme. Thus, circulating Vitamin D is less potent and appears to require compensation of higher Vitamin D_2 or Vitamin D_3 intake or increased sun exposure to help prevent age-related hip and other fractures.[2,4,5]

Excess Vitamin D is stored in the liver. It has recently been shown that humans can tolerate much higher levels of Vitamin D intake without experiencing toxicity than previously believed to be true. In fact, higher levels (i.e., 1,000 I.U. or more per day) may be advantageous in people living above or below the 40th degree latitude, where sunlight intensity is insufficient for long periods of the year to maintain optimal levels of serum Vitamin D (approximately 100 nmol/L) that is associated with less osteoporosis, certain cancers and multiple sclerosis.[2,6,7,8]

Vitamin D formed under the skin as well as 25-hydroxyvitamin D_3 are transported through the blood attached to Vitamin D plasma binding protein, which is synthesized in the liver.[1]

Functions

Vitamin D in the bloodstream stimulates the intestinal absorption of calcium and phosphorous (stimulates synthesis of calcium-binding protein in intestinal cells).

Vitamin D regulates the metabolism of calcium and phosphorous, which is vital for many functions including neuromuscular function, and mineralization of bone and teeth.[1]

Vitamin D is involved in cellular differentiation of many tissues. Vitamin D receptors have been found on intestinal epithelial cells, renal cells, bone cells, skin cells, breast cells, and cells in the pancreas, connective tissue and parathyroid gland.[1,9]

Vitamin D acts directly on bone aiding bone formation and in times of need, it stimulates the release of calcium from bone to help maintain blood calcium within the normal range; a function it shares with parathyroid hormone.[1]

Vitamin D modulates immune system function, which appears to be important in resistance to infectious diseases and possibly multiple sclerosis prevention.[2,10,11,12,21]

Age Group and Gender	(International Units I.U.)
0-6 months	300
6 months-10 years	400
Males 11-24	400
Males 25 and older	200
Females 11-24	400
Females 25 and older	200
Pregnant Women	400
Lactating Women	400 [1]

RDA (Vitamin D) – one I.U. equals 0.025 mcgs.

N.B. recent evidence suggests that older adults can reduce their risk of bone fractures by supplementing with 600-800 I.U. of Vitamin D per day to compensate for the drop off in conversion of 25 hydroxyvitamin D_3 to 1, 25-dihydroxyvitamin D_3 that accompanies aging.[5,13]

Overt Vitamin D Deficiency

1. Rickets: lack of Vitamin D results in inadequate absorption of calcium and phosphorous, and consequently, faulty mineralization of bones and teeth. In children, this results in skeletal malformations from soft bones (i.e. knock knees, skull deformities).
2. Osteomalacia: in adults Vitamin D deficiency causes osteomalacia (bone softening) or adult rickets. The most common symptoms are weakening of the bone due to an increased porosity and decreased density. This can result in pain the bones in the leg and lower back, difficult walking and bone fractures.

N.B. The main cause of primary Vitamin D deficiency is lack of sunlight, hence milk fortification with Vitamin D is used in many countries to help safeguard against frank Vitamin D deficiency. In the U.S., one quart of milk is fortified with 400 I.U. of Vitamin D.[1]

Supplementation Studies and Clinical Applications

Osteoporosis Prevention and Management

Human intervention studies demonstrate that postmenopausal women and older individuals can reduce their risk of hip fractures by approximately 43 percent with Vitamin D supplementation at 800 I.U.[2,4,5,13]

Cancer Prevention

Individuals with higher blood levels of Vitamin D (at or above 100 nmol/L) tend to have a lower risk of colon, breast and prostate cancer. In subjects living above or below the 40th latitude, Vitamin D supplementation of 400-1,000 I.U. per day is often required to achieve this blood level of Vitamin D. Generally speaking, 400 I.U. of Vitamin D supplementation raises serum 25-hydroxyvitamin D levels by about 45 nmol/L.

N.B. In experimental studies, Vitamin D has been shown to suppress cancer cell proliferation, induce cancer cell apoptosis and differentiation, demonstrating a strong potential role in the prevention and management of colon, breast and prostate cancer.[2,6,7,8,14-17]

Dosage Ranges

Prevention of Osteoporosis and possibly certain cancers in adults over 40 years of age: consider 400-1,000 I.U. per day, especially if living in regions above or below the 40th degree latitude.[2,5,8,11,13-17,19,20]

Vitamin D Side Effects and Toxicity

Hypercalcemia is always accompanied by a serum 25 hydroxyvitamin D concentration of greater than 220 nmol/L.

Most authorities recommend that adults not supplement with more than 1,000 I.U. per day (of Vitamin D), however, evidence suggests that levels as high as 4,000 I.U., per day is non-toxic and may actually be beneficial in osteoporosis prevention and management, as well as for other health-promotion purposes (see reference 2 for complete details of this position).[1,2] In fact, of all published cases of Vitamin D toxicity for which a Vitamin D amount is known, only one occurred at a dose under 40,000 I.U. per day.[2] Nevertheless, people wishing to take more than 1,000 I.U. per day for long periods of time require proper monitoring of block levels and liver function tests.

People with hyperparathyroidism should not take Vitamin D supplements without consulting a physician, nor should people with sarcoidosis.

Signs and symptoms of Vitamin D toxicity include headaches, nausea, vomiting, polyuria, polydipsia, weight loss, kidney stones, calcification of soft tissues and some other more rare symptoms (i.e., blindness, deafness).[1,2]

Drug-Nutrient Interactions

It is well known that cortisone or predisone therapy (glucocorticoids) interfere with the metabolism of Vitamin D and are associated with increased risk of osteoporosis. Barbituates and anticonvulsants also cause increased degradation of Vitamin D and its metabolites[1] and increase osteoporosis risk.[22,23]

Other drugs that reduce Vitamin D nutritional status include:

Allopurinol[19]

Bile Acid Sequestrants (eg. Cholestyramine and colestipol)[18,24]

Cimetidine and other H-2 Antagonists[18,25]

Oral Contraceptives[18]

Heparin[18]

Hydroxychloroquine[18]

Indapamide[18]

Isoniazid[18,26]

Mineral oil[18,27]

Neomycin[18]

Thiazide Diuretics[18]

Rifampin – may reduce blood vitamin D levels by 70%[28]

Orlistat – reduces blood levels of Vitamin D[29]

Vitamin D supplements may antagonize the calcium channel blocker drug known as Verapamil, which is used to treat angina pectoris, heart arrhythmias, and hypertension.[18]

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Vitamin E

Introduction

Vitamin E is the name given to a group of fat-soluble compounds, which include tocopherols and tocotrienols. The term "tocopherol" comes from the Greek word meaning "to bear offspring". A Vitamin E deficiency in rats results in infertility and the re-introduction of Vitamin E to the diet corrects this problem. The most abundant and potent form of Vitamin E is d-alpha tocopherol (natural Vitamin E). Vitamin E is destroyed by light and oxygen. At the same time, however, it protects Vitamin A, Vitamin C and carotenes in food from oxidative destruction.

Absorption and Metabolism

As a fat-soluble nutrient, Vitamin E is absorbed from the intestinal tract via chylomicrons and lymph. It is carried in the blood by lipoproteins (i.e., VLDL and LDL) and is stored primarily in adipose tissue, with smaller amounts found in the liver, muscle tissue and adrenal glands.

Vitamin E is released into the circulation whenever fat is mobilized. Its metabolites are excreted both in urine and in feces.

Approximately 50 to 85 percent of Vitamin E is absorbed from the intestinal tract into the bloodstream, provided there is some fat present in the intestinal tract.

Recommended Daily Allowance (Vitamin E)

Age Group	International Units
0-12 months	4.5-6.0
1-10 years	9-10.5
Males 11 and older	15
Females 11 and older	12
Pregnant Females	15
Lactating Females	18

Equivalents

1 mg of d-alpha tocopherol (natural) = 1 alpha tocopheral equivalent (alpha T.E.) = 1.49 IU[1]

The "d" form denotes natural Vitamin E and is also known as RRR-alpha tocopherol.

The "dl" form denotes synthetic Vitamin E and is also known as all-race-alpha tocopherol.

Relative Biological Activity of Various Tocepherols[2]

Compound	Activity (IU of Compound Per Milligram)
d-alpha-tocopherol (natural)	1.49
dl-alpha-tocopherol (synthetic)	1.1
d-beta-tocopherol	0.6
d-gamma-tocopherol	0.15-0.45
d-alpha-tocotrienol	0.3
• d-beta-tocopherol	• 0.015

N.B. In the human body, only the d-form is recognized (natural Vitamin E). Although the l-form has antioxidant activity, it may actually inhibit the d-form from entering cell membranes. Thus most authorities recommend supplementation using only natural Vitamin E (d-alpha-tocopherol).[3,4,5] Recent studies suggest that natural Vitamin E is twice as bioactive as the synthetic form.[6]

Vitamin E Deficiency

Newborn infants have low tissue concentrations of Vitamin E because there is little transfer across the placenta. A haemolytic anemia can result in infants if their serum tocopherol levels are less than 0.5 mg/dl. A severe eye disorder called retrolental fibroplasia may also result.

This problem usually arises due to infant formulas high in polyunsaturated fats and containing iron. Because of formula changes, it is now rarely seen.

In adults Vitamin E deficiency can occur in:

Fat malabsorption syndromes, such as sprue, celiac disease, cystic fibrosis, and post-gastrectomy syndrome.

Sickle cell anemia and thalassemia.

Hemodialysis patients.

Symptoms of Vitamin E deficiency in adults include nerve damage, muscle weakness, poor coordination, involuntary movement of the eyes, red blood cell rupture leading to anemia (haemolytic anemia).

This suggests a neurological role for Vitamin E, in addition to its known antioxidant function.[1,2,7]

Functions

Antioxidant

As a fat-soluble antioxidant Vitamin E has been shown to protect various structures from oxidation and free radical damage, including:

a. LDL-cholesterol[8]
b. Cell Membrane structure[9]
c. Thymus gland[10]
d. White blood cells[10]
e. Lens and macula of the eye[11,12]
f. Nerve cells, including the brain[13]

Prostaglandin Synthesis

Vitamin E modulates prostanoid or eicosanoids biosynthesis. Prostanoids are compounds derived from polyunsaturated fatty acids and include thromboxanes, prostacyclins, leukotrienes and three series of primary prostaglandins.[1] By down regulating the conversion of arachidonic acid to the pro-inflammatory prostaglandin series 2, Vitamin E supplementation has been shown to reduce inflammatory conditions and also to decrease platelet clotting, although this effect may also be attributable to Vitamin E's ability to directly antagonize the clotting function of Vitamin K.[1,14,15]

Nervous system function

As Vitamin E deficiency results in nerve damage, Vitamin E is required to preserve the normal function of nerve cells.[6]

Male Fertility

Vitamin E deficiency or marginal deficiency can result in decreased male fertility, which can be reversed via Vitamin E supplementation.[16]

Supplementation Studies and Clinical Applications

Cardiovascular Disease

Substantial evidence suggests that Vitamin E supplementation can reduce the risk of coronary heart attack, stroke, angina, peripheral vascular disease and advancing atherosclerosis. The mechanisms of protection appears to be the following:

Decreased LDL-cholesterol oxidation: decreases oxidation of LDL cholesterol and thereby, reduces its uptake by macrophages and their subsequent transformation into foam cells. Foam cells are part of the atherosclerotic plaque and represent the primary mechanism by which cholesterol becomes incorporated into the atherosclerotic process, which narrows arteries throughout the body.[8,17,18]

Inhibition of Excessive Platelet Aggregation: via its effects on prostaglandin synthesis, Vitamin E appears to reduce the synthesis of thromboxanes A_2, which increases platelet coaguability and it has been shown to antagonize the action of Vitamin K, which is a procoagulant. Thus, Vitamin E acts like a natural blood thinner, but with far less potency than aspirin or warfarin (coumadin).[1,15,19]

Inhibits the Proliferation of smooth muscle to grow into the lumen of the artery: as part of the atherosclerotic process platelets release a growth factor which normally encourages smooth muscle and connective tissue to proliferate and grow into the lumen of the artery, further reducing blood flow and narrowing arteries. Vitamin E has been shown to inhibit smooth muscle proliferation in experimental studies.[20,21]

Heart Disease Studies: a number of large prospective studies have demonstrated that Vitamin E supplementation of 100 I.U. or more is associated with approximately a 40 percent reduction in risk of heart disease compared to subjects not taking Vitamin E supplements or supplementing at a dosage below 100 I.U. per day.[22,23,24]

Intervention trials with high risk heart disease patients have also revealed that the use of Vitamin E supplementation of 100 IU or more per day, significantly reduced risk of heart disease, heart attack and fatal myocardial infarction. In the Cholesterol Lowering Atherosclerosis Study of 156 men (age 40-59) post bypass surgery, 100 IU or more of Vitamin E per day significantly decreased restenosis of coronary arteries, as evidenced by angiography studies after several years of follow-up.[25]

In the Cambridge Heart Antioxidant Study (CHAOS) supplementation with 400 or 800 I.U. of Vitamin E reduced risk of non-fatal heart attacks by 75 percent in high-risk patients as compared to those given the placebo. The beneficial effects were apparent after one year.[26] The Finnish Alpha-Tocopheral, Beta-Carotene Cancer Prevention Study (ATBC) also showed a reduction in heart disease in subjects taking Vitamin E supplements compared to the placebo group.[27] However, Vitamin E supplementation showed no benefit in the Heart Outcomes Prevention Evaluation Study.[28]

Angina: in the ATBC study mentioned above, Vitamin E supplement users also demonstrated a reduction in angina.[27] Other studies have shown that Vitamin E has been effective in patients with existing angina pectoris.[20,29]

Intermittent Claudication: intermittent claudication has also been improved with Vitamin E supplementation.[20,30-33]

Alzheimer's Disease

Emerging evidence links free radical damage to brain cells with the development and progression of dementia and Alzheimer's disease. In the Alzheimer's Disease Cooperative Study a daily dosage of 2,000 I.U. of Vitamin E slowed the functional deterioration of Alzheimer's patients. Vitamin E appears to protect nerve cells from A beta-amyloid protein-induced oxidative damage and neurotoxicity.[13,34,35]

Prostate Cancer Prevention

Subjects in the ATBC study (mentioned above) taking 50 mg of Vitamin E (75 I.U.) showed a 32 percent decrease in the incidence of prostate cancer and a 41 percent decrease in prostate cancer death, compared to those taking the placebo.[36]

Post Cancer Treatment

In the study by Lockwood a cocktail of antioxidant supplements (including Vitamin E-2,500 I.U.) and other nutrients reduced the progression of breast cancer in women with existing axillary lymph node involvement.[37]

Primary Cancer Prevention

Results from the US National Institute on Aging study showed a 22 percent decrease in risk of cancer death compared to non-Vitamin E supplement users.[38]

Vitamin E exhibits a number of cancer prevention effects beyond antioxidant function, which include antiproliferative and apoptosis (programmed cell death) effects on certain human cancer cell lines as well as other protective functions.[39-42]

In the Iowa Women's Health Study women with the highest intake of Vitamin E (primarily supplementation) had a 30 percent lower incidence of colon cancer compared to those demonstrating a low Vitamin E intake.[43] Similar findings exist for cervical cancer (40 percent reduction in risk with high Vitamin E intake).[44]

The Iowa Women's Health Study has more recently demonstrated that higher Vitamin E intake may also reduce risk of oral, pharyngeal, esophageal and gastric cancers.[45] Vitamin E also blocks the formation of cancer causing nitrosamines in the human intestinal tract,[68] in a similar fashion as Vitamin C.

Fibrocystic Breast Disease

Some studies have shown that 600 I.U. of Vitamin E taken as a supplement can reverse fibrocystic breast disease.[46,47]

Cataracts and Macular Degeneration

Several preliminary studies reveal that Vitamin E supplementation (usually in combination with other antioxidants) can reduce the risk of cataracts and halt or slow the progression of macular degeneration of the eye (some cases showed improved visual acuity) in intervention trials.[48,49,50]

Male Fertility

In one study infertile males (n=52) treated with 600-800 I.U. of Vitamin E demonstrated improvement in sperm quality; eleven were able to impregnate their spouses following Vitamin E treatment.[51]

Tardive Dyskinesia

Drugs that treat schizophrenia may trigger Tardive Dyskinesia due possibly to free radical damage to nerve cells. Vitamin E supplementation at 1,600 I.U. has been used successfully to treat Tardive Dyskinesia in these patients.[52,53,54]

HIV/AIDS

A nine year study involving 311 HIV-positive men showed that those patients with highest Vitamin E intakes had a 35 percent decrease in risk of progression to AIDS when compared to the lower intake group.[55] Other studies suggest a similar protective effect.[56,57]

Hepatitis C

A 1997 preliminary study of 23 hepatitis C patients treated with 400 I.U. of Vitamin E, twice per day, revealed significant improvement in 11 of 23 patients as demonstrated by clinical testing of liver function.[58]

Asthma

A preliminary study has shown that supplementation with 400 I.U. of Vitamin E and 500 mg of Vitamin C increased peak flow capacity by 18 percent in a trial of 17 asthma sufferers (treadmill testing with peak flow lung function tests).[59]

Rheumatoid Arthritis and Osteoarthritis

Several studies have shown that Vitamin E supplementation at 400 I.U. per day or 895 IU, twice per day can reduce symptoms and signs of rheumatoid arthritis, when compared to placebo.[14, 60]

Osteoarthritic patients have also shown benefit from Vitamin E supplementation.[61,62]

Diabetes

Vitamin E supplementation has been shown to improve insulin sensitivity (900 I.U. per day) in elderly subjects, as well as fasting glucose, triglycerides and LDL:HDL ratio.[63] Vitamin E supplementation of 100 I.U. per day significantly lowered lipid peroxidation products and lipid levels in diabetic patients.[64]

Exercise-Induced Free Radical Damage

Studies are demonstrating that Vitamin E daily supplementation (400 I.U to 1,200 I.U.) reduces free radical damage induced by aerobic and strength training exercise, preserving muscle membrane structure and reducing muscle inflammation.[65]

Diabetes

Vitamin E studies with diabetic patients have generally revealed a number of significant benefits, which include:

Decreased LDL-Cholesterol oxidation
Improved insulin sensitivity
Lower triglycerides
Improved LDL:HDL ratio
Improved glucose tolerance
Lower fasting insulin levels.

In two trials, a daily dosage of 1,350 I.U. of Vitamin E was used for up to 4 months.[66,67] However, in one trial a dosage as low as 100 I.U. per day of Vitamin E was shown to significantly lower lipid peroxidation and lipid levels over a three month period.[64]

Premenstrual Syndrome

Vitamin E supplementation (400 I.U.) has been shown to improve various symptoms in PMS. In one double-blind trial a success rate of 33 percent was realized with respect to physical symptoms, and 38 percent with anxiety.[68,69]

Parkinson's Disease

Oxidative damage has been shown to be a contributing factor to Parkinson's disease. A preliminary study demonstrated that Vitamin E supplementation significantly showed the progression of the disease. More recently, a double-blind study showed no benefit with Vitamin E supplementation. Further trials are underway.[70,71]

Restless Leg Syndrome

Vitamin E supplementation has been shown to be useful in some studies.[72,73]

For most conditions reviewed above, Vitamin E supplementation of 100-400 I.U. has been shown to provide the stated benefits. Higher doses have been used in the following cases:

Dosage Ranges

Alzheimer's Disease[13]	2,000 I.U. per day
Post Cancer Treatment[37]	2,500 I.U. per day
Fibrocystic Breast Disease[46,47]	600 I.U. per day
Male Fertility Treatment[51]	800 I.U. per day
Tardive Dyskinesis (requires medical monitoring)[52,53,54]	1,600 I.U. per day
HIV/AIDS[69]	400-800 I.U. per day
Hepatitis C[58]	400 I.U., twice per day (800 I.U)
Rheumatoid Arthritis[60]	400-900 I.U. per day
Parkinson's Disease (requires medical monitoring)[74]	3,200 I.U. Vitamin E and 3,000 mg Vitamin C
Diabetes[64,66,67]	100-3,000 I.U.
• Osteoarthritis – Vitamin E supplementation has been shown to reduce symptoms of osteoarthritis in both single and double-blind trials at daily dosage of 400-800 I.U. per day.[61,62]	• 400-800 IU
• Restless Legs Syndrome – several case reports have reported improvement with Vitamin E supplementation at 300-400 I.U. per day, although it may take up to three months to realize the benefit.[72,73]	• 300-400 IU

Adverse Side Effect and Toxicity

Vitamin E exhibits very little toxicity, even at high doses (i.e., 3,200 I.U. per day) in two-year trails.[75] At doses higher than 800 I.U. per day, Vitamin E may increase the risk of a bleeding disorder. At higher doses it may infrequently cause high blood pressure, and abdominal pain.[76]

Increasing the dosage slowly over time may overcome the high blood pressure response that occurs in some patients (Author's note). Begin at 100 I.U. per day.

Drug-Nutrient Interactions

Vitamin E supplementation can potentiate the anti-coagulant effect of aspirin, warfarin or coumadin at does above 400 I.U. In this case, a bleeding disorder may result. The general consensus is that Vitamin E at a daily dosage up to 400 I.U. can be taken concurrently with these medications.[77,78]

Drugs that deplete Vitamin E include:

- Bile Acid Sequestrants
- Gemfibrozil
- Isoniazid
- Mineral oil
- Anticonvulsants (phenytoin, carbamazepine and Phenobarbital)
- Orlistat - decreases Vitamin E absorption
- Chitosan - decreases Vitamin E absorption if taken at the same time[79-89]

Vitamin E can serve a supportive interaction with the following drugs:

- Allopurinol
- Cycolsporin
- Griseofulvin
- Simvastatin
- Sodium fluoride[90]

Neomycin impairs utilization of Vitamin E. Vitamin E can help reduce the side effects of the following drugs:

- Amiodarone
- Anthralin
- Benzamycin
- Chemotherapy
- Cyclophosphamide
- Dapsone
- Haloperidol
- Lindane
- Risperidone[76,90]

High intakes of polyunsaturated fats can decrease Vitamin E levels in the body, thus increasing Vitamin E requirements.[1]

Pregnancy and Lactation

During pregnancy and lactation, the only supplements that are considered safe include standard prenatal vitamin and mineral supplements. All other supplements or dose alterations may pose a threat to the developing fetus and there is generally insufficient evidence at this time to determine an absolute level of safety for most dietary supplements other than a prenatal supplement. Any supplementation practices beyond a prenatal supplement should involve the cooperation of the attending physician (i.e., magnesium and the treatment of preeclampsia.)

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Vitamin K

Introduction

The "K" in Vitamin K stands for koagulation, the Danish spelling of the word for blood clotting, for it was discovered by a Danish scientist, Henrik Dam, in 1929.

Vitamin K is actually a group of yellowish crystalline (chemically pure) compounds belonging to a family of substances called quinones. There are at least three forms of Vitamin K. The naturally occurring vitamins are K1 (phylloquinone), which occurs in green plants and K2 (menaquinone), which is formed as the result of bacterial synthesis in the intestinal tract. The fat-soluble synthetic compound, menadione (K3) is about twice as potent biologically as the naturally occurring Vitamins K1 and K2 on a per microgram basis. Humans and animals convert menadione to menaquinone by adding a long side chain.

Absorption and Metabolism

As a fat-soluble vitamin, Vitamin K requires bile acid and pancreatic juice for its absorption. Therefore, fat in the gut must be present to stimulate Vitamin K absorption. Vitamin K is incorporated into chylomicrons in intestinal mucosal cells and is carried to the liver via chylomicrons.

Functions

1. **Blood clotting**

   In the liver Vitamin K functions as an essential cofactor for the carboxylase enzyme that converts specific glutamic acid residues of precursor proteins to a new amino acid, alpha-carboxyglutamic acid (Gla) in the completed proteins. These proteins include the Vitamin K-dependent blood clotting factors prothrombin (factor II) and factors VII, IX and X. Thus, a Vitamin K deficiency or the presence of an antagonist (i.e., coumarin or some snake venoms) will prolong blood-clotting time.

2. **Bone Health and Osteoporosis Prevention**

   Vitamin K – dependent carboxylase enzyme is also required to convert glutamic acid residues into alpha-carboxyglutamic acid (Gla) in the synthesis of osteocalcin found in bone and kidney.[1]

   Vitamin K deficiency can lead to inadequate osteocalcin levels and impaired bone mineralization. Some studies have reported low Vitamin K levels in osteoporotic patients with fractures and/or lower bone mineral density.[2,3,4]

   The presence of Vitamin K_1 in green leafy vegetables may be one of the protective factors of a vegetarian diet against osteoporosis, which is a common finding in epidemiological studies.[5]

Vitamin K Recommended Daily Allowance

For adults the recommendation is 70-140 micrograms per day to ensure adequate status.

Age Group and Gender	Micrograms
0-6 months	5
6-12 months	10
1-3 years	15
4-6 years	20
7-10 years	30
Males 11-14 years	45
Males 15-18 years	65
Males 19-24 years	70
Males 25 and older	80
Females 11-14 years	45
Females 15-18 years	55
Females 19-24 years	60
Females 25 and older	65
Pregnant females	65
Lactating females	65

N.B. Since bacterial synthesis usually provides at least half the required amount of Vitamin K, there is usually little difficulty in acquiring the required dietary amount that is necessary.[1]

An average mixed diet provides 300 to 500 micrograms of Vitamin K daily.[6] However, men and women aged 18-44 years often ingest less than the recommended level of Vitamin K.[8,9]

Vitamin K Deficiency

Hemorrhagic Disease of the Newborn

Little Vitamin K from the mother is transferred via the placenta to the developing fetus, and the normal intestinal bacteria that synthesize Vitamin K do not become established until about a week after birth. Hence, "hemorrhagic disease of the newborn" is not uncommon – a disease manifested by abnormal bleeding.

Therefore, it is necessary at times to administer Vitamin K intramuscularly to the baby upon delivery as a preventative measure against this disease (1mg of Vitamin K_1 immediately after birth).[1] This is a common practice.

Another approach used in Germany and sanctioned by the German Paediatric Society recommends giving oral Vitamin K at a dosage of 5mg twice weekly for the first 3 months of life.[7]

Supplementation Studies and Clinical Application

1. **Osteoporosis**

   It may be useful to supplement with 150-500 micrograms of Vitamin K to help prevent or treat osteoporosis in some instances (i.e., poor dietary intake of Vitamin K, fat malabsorption or if patient is taking drugs that deplete Vitamin K status).[10]

2. **Excessive Menstrual Bleeding and Bruising**

   In these cases Vitamin K status should be determined and supplementation with 150-500 micrograms of Vitamin K should be considered as part of the nutrition plan.[10]

   It is known that doses of Vitamin K at 1 to 2 mg will correct a frank Vitamin K deficiency in most cases.[1]

   N.B. Vitamin K supplementation is contraindicated if the patient is taking warfarin.[12,13]

Adverse Side Effects and Toxicity

Excessive doses of synthetic Vitamin K (mendione) can produce haemolytic anemia and jaundice in infants. Thus, mendione is no longer permitted in over-the-counter preparations. The water-soluble forms of Vitamin K have a greater safety margin and should be used when Vitamin K supplements are indicated.[1]

Drug-Nutrient Interactions

2. **A large number of drugs deplete or interfere with Vitamin K or hinder its activity, respectively. These include:**
   a. Anitbiotics - N.B. The exception is with the antibiotic drug ofloxacin, whereby Vitamin K depletion does not occur.[11,14]
   b. Anticonvulsants[11,15,16]
   c. Bile Acid Sequestrants
   d. Corticosteroids
   e. Oral Corticosteroids[11]
   f. Isoniazid[11]
   g. Mineral Oil[11,18]
3. **Contra-indication**

   Since Vitamin K administration reverses the anticoagulant effects of Warfarin, people taking Warfarin should avoid Vitamin K – containing supplements, unless specifically directed by their prescribing doctor. Even the sudden ingestion of increased quantities of Vitamin K-containing vegetables (broccoli, brussels sprouts, kale, spinach, parsley, etc.) can antagonize the effects of Warfarin.[12,13,19,20]

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