Vitamins in aging, health, and longevity

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Abstract: Evidence of epidemiological associations of vitamins and disease states have been found for nine vitamins. In observational studies, people with a high intake of antioxidant vitamins by regular diet or as food supplements generally have a lower risk of major chronic disease, such as myocardial infarction or stroke, than people who are low consumers of antioxidant vitamins. Prospectively, folate appears to reduce the incidence of neural tube defects. Vitamin D is associated with a decreased occurrence of fractures when taken with calcium. Zinc, betacarotene, and vitamin E appear to slow the progression of macular degeneration, but do not reduce the incidence. Vitamin E and lycopene may decrease the risk of prostate cancer. In other randomized controlled trials, the apparent beneficial results of a high intake of antioxidant vitamins seen in observational studies have not been confirmed. There is increasing concern from these trials that pharmacological supplementation of vitamins may be associated with a higher mortality risk.

Keywords: vitamins, epidemiological, antioxidant, carotenoids

Introduction

Food is essential to survival and health. Our ability to expend energy depends on an adequate intake of protein and calories. However, nutritional deficiency diseases can occur even when adequate calories are available. Historically, physicians have observed that a number of peculiar disease states such as scurvy, pellegra, and beriberi were directly related to dietary intake. These diseases were also found in the presence of adequate calorie and protein intake. These strange nutritional deficiency states perplexed researchers until the turn of the century.

A brief history of vitamins

With the ability to synthesize organic compounds around the turn of the 19th century, researchers believed that food could be produced in the laboratory as well as in nature. An "adequate diet" could be manufactured by combining purified protein, carbohydrates, and fats with inorganic salts and water. Experimental animals fed purified organic compounds failed to thrive. In an early experiment in 1881, Lunin found that young mice did not grow when fed an apparently adequate amount of purified organic compounds. In 1905, Pickelharing found that substitution of small amounts of milk in place of water allowed animals to survive on a purified organic compound diet. He concluded that there was some "unknown substance" in the milk without which the animals could not survive.

A peculiar polyneuritis, later identified with beriberi, developed in chickens fed on a diet of polished rice. In 1884, Christine Eijkman demonstrated that this polyneuritis could be prevented or cured in fowl by feeding them unpolished rice instead of polished rice. Following the current vogue, Eijkman believed that a "germ" was neutralized by "something" in the husks of unpolished rice. In 1911, Casimir Funk proposed that the Eijkman factor was not a germ, but a pyrimidine compound.

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The pyrimidine compound cured beriberi when fed to pigeons. Since the compound appeared to be "vital" to life, and since he thought it was an amino acid, he named the compound a "vitamine". The name stuck, although the final "e" was dropped when it was later shown that vitamins were not amines. A vitamin was recognized as an organic compound present in the diet necessary for normal metabolic functioning.

Scurvy was known to be cured by lemons and limes by 1753, but was not recognized as a nutritional deficiency. A guinea pig model of scurvy was developed in 1907, rapidly leading to a demonstration that scurvy could be prevented by addition of a "water-soluble factor C" to the diet. The organic compound was isolated and named ascorbic acid in 1928. This finding of a minute amount of a substance essential to health in the diet resulted in the award of the 1937 Nobel Prize in Chemistry to research with ascorbic acid.

The ability of biochemists to produce a compound in the laboratory identical to the "natural" substance led to the availability of nutritional supplements aimed at preventing disease. Widespread use of these compounds has had a profound effect in worldwide prevention, such as vitamin D supplementation of milk. These "vitamins" were essential for normal metabolic functioning and the consumption of an abundance of vitamins could possibly prevent disease.

Vitamins and aging

Theories of cellular and organism aging developed in the middle twentieth century. One of the leading theories proposed that damage to cellular mechanisms and tissues occurs because of chronic damage resulting from oxidative stress on the organism due to free oxygen radicals. Endogenous oxidative damage to proteins, lipids, and DNA is thought to be an important etiologic factor in aging and the development of chronic diseases such as cancer, atherosclerosis, and cataract formation. The harm associated with these diseases is likely to occur only after the production of reactive oxygen species exceeds the body's or cell's capacity to protect itself and effectively repair oxidative damage. There is a hypothesized effect, which relates antioxidant vitamins and aging. Certain "antioxidant" compounds might "scavenge" these damaging free oxygen radicals and prevent cellular destruction and aging. Vitamin C, vitamin E, and betacarotene, often referred to as "antioxidant vitamins", have been suggested to limit oxidative damage in humans and lower the risk of certain chronic diseases.

This hypothesis has driven a large number of epidemiological studies and clinical trials examining the efficacy of antioxidant vitamins. The mechanism by which certain vitamins may lower in vivo oxidative damage to lipids, proteins, or DNA is not known. The current evidence is insufficient to conclude that antioxidant vitamin supplementation materially reduces oxidative damage in humans (McCall and Frei 1999), with the exception of supplemental vitamin E and possibly vitamin C being able to significantly lower lipid oxidative damage in both smokers and non-smokers.

Aging is associated with increased risk for low vitamin consumption. In the United States, total energy intake decreases substantially with age: by 1000 kcal–1200 kcal in men, and by 600 kcal–800 kcal in women in the seventh decade. This results in concomitant declines in most nutrient intakes. Lower food intake among the elderly has been associated with lower intakes of calcium, iron, zinc, B vitamins, and vitamin E. This low energy intake or low nutrient density of the diet may increase the risk of diet-related illnesses. Fifty percent of older adults have a vitamin and mineral intake less than the recommended daily intake (RDI), while 10%–30% have subnormal levels of vitamins and minerals (Wakimoto 2001). Populations at high risk for inadequate vitamin intake include elderly people, vegans, alcohol-dependent individuals, and patients with malabsorption.

Older adults tend to consume less energy-dense sweets and fast foods, and consume more energy-dilute grains, vegetables, and fruits. Daily volume of foods and beverages also declines as a function of age. Physiological changes associated with age, including slower gastric emptying, altered hormonal responses, decreased basal metabolic rate, and altered taste and smell may also contribute to lowered energy intake. Other factors such as marital status, income, education, socioeconomic status, diet-related attitudes and beliefs, and convenience likely play a role as well (Thomas 2002). Many age-related nutritional problems may be remedied to an extent by providing nutrient-dense meals through home delivery or meal congregate programs (Drewnowski and Shultz 2001).

Antioxidant vitamins

The vitamin A and carotienoid family

The carotenoids are a diverse group of more than 600 naturally occurring pigments. Natural sources include yellow, orange, and red plant compounds such as carrots and green leafy vegetables. Humans cannot synthesize

carotenoids and exclusively depend on dietary intake for these micronutrients. Betacarotene and lycopene are the major dietary carotenoids. Lycopene is a natural pigment synthesized by plants and microorganisms but not by animals. It occurs in the human diet predominantly in tomatoes and processed tomato products. It is a potent antioxidant and the most significant free radical scavenger in the carotenoid family. There is no known deficiency state for carotenoids themselves and no recommended daily intake. Betacarotene can be converted to vitamin A, whereas lycopene cannot. All of the carotenoids are antioxidants and approximately 50 are considered vitamins because they have provitamin A activity. Vitamin A refers to preformed retinol and the carotenoids that are converted to retinol. Preformed vitamin A is found only in animal products, including organ meats, fish, egg yolks, and fortified milk. More than 1500 synthetic retinoids, analogs of vitamin A, have been developed. The current RDI for vitamin A is 1500 micrograms/L (5000 IU).

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble vitamin widely found in citrus fruits and raw leafy vegetables, citrus fruits, strawberries, melons, tomatoes, broccoli, and peppers. Humans cannot synthesize vitamin C and deficiency results in scurvy.

Vitamin E

Vitamin E occurs in eight natural forms as tocopherols (alpha, beta, gamma, and delta) and tocotrienols (alpha, beta, gamma, and delta), all of which possess potent antioxidant properties. Gammatocopherol is the predominant form of vitamin E in the human diet, yet most studies have focused on alphatocopherol, which is the type found in most over-the-counter supplements. One reason for this is that alphatocopherol is biologically more active than gammatocopherol. Vitamin E deficiency is rare and is seen primarily in special situations resulting in fat malabsorption, including cystic fibrosis, chronic cholestatic liver disease, abetalipoproteinemia, and short bowel syndrome.

Other essential vitamins

Vitamin B12

Vitamin B12 deficiency occurs in 5%–20% of older persons (Andres et al 2004), but it is often unrecognized because the clinical manifestations are subtle (Thomas 2004). Causes of the deficiency include malabsorption of the vitamin (60% of all cases), pernicious anemia (15%–20% of all cases), and insufficient dietary intake. Measurement of vitamin B12 and folate concentrations will determine anemia due to these causes in the majority of cases. Confirmation of vitamin B12 deficiency in those patients who have values in the lower normal range should be obtained, since about 50% of patients with subclinical disease may have normal B12 levels. A more sensitive method of screening for vitamin B12 deficiency is measurement of serum methylmalonic acid and homocysteine levels, which are increased early in vitamin B12 deficiency. A homocysteine level will be elevated in both vitamin B12 and folate deficiencies, but a methylmalonic acid level will be elevated only in vitamin B12 deficiency. Renal failure is the only other confounding cause of an elevated methylmalonic acid concentration.

Folic acid

Folate and vitamins B6 and B12 are required for the conversion of homocysteine to methionine. Increases in homocysteine have been associated with increased coronary heart disease risk in observational trials. Inadequate folate status is associated with neural tube defect in children (Paulozzi et al 2001) and with colon cancer (Giovannucci et al 1998). Folate occurs naturally in a variety of foods, including liver; dark-green leafy vegetables such as collards, turnip greens, and romaine lettuce; broccoli and asparagus; citrus fruits and juices; whole grain products; wheat germ; and dried beans and peas such as pinto, navy, and lima beans, chickpeas and black-eyed peas. Effective from 1998, the Food and Drug Agency required manufacturers to add from 0.43 mg–1.4 mg of folic acid per pound of product to enriched flour, bread, rolls and buns, farina, corn grits, cornmeal, rice, and noodle products.

Vitamin D

Vitamin D occurs naturally in animal foods as the provitamin cholecalciferol. This requires conversion in the kidney to the metabolically active form, calcitriol. Vitamin D is not a true vitamin since humans are able to synthesize it with adequate sunlight exposure. By photoconversion, 7-dehydrocholesterol becomes previtamin D3, which is metabolized in the liver to the major circulating form of vitamin D: 25-hydroxyvitamin D3. In the kidney, this is converted to 2 metabolites, the more active one being 1,25-dihydroxyvitamin D3. Food sources include fortified milk, saltwater fish, and fish-liver oil.

Thiamin

Thiamine pyrophosphate is a coenzyme for pyruvate dehydrogenase, a-ketoglutarate dehydrogenase and

transketolase. Thiamine deficiency results in beriberi, a syndrome that includes symptoms of weight loss, emotional disturbances, impaired sensory perception, weakness, and heart failure. Thiamine is found in fortified breads, cereals, pasta, whole grains (especially wheat germ), lean meats (especially pork), fish, dried beans, peas, and soybeans. Dairy products, fruits, and vegetables are not very high in thiamine, but when consumed in large amounts, they become a significant source.

Pyridoxine

Vitamin B6 has been associated with cardiovascular risk and lipids. Vitamin B6 is found in a wide variety of foods including fortified cereals, beans, meat, poultry, fish, and some fruits and vegetables.

Riboflavin

Deficiency is rare in the United States due to widely available sources of this vitamin. Lean meats, eggs, legumes, nuts, green leafy vegetables, dairy products, and milk provide riboflavin in the diet. Breads and cereals are often fortified with riboflavin. Other than deficiency states, association with disease is unknown.

Minerals

Approximately 15 inorganic elements are required in minute amounts. In humans, clinically symptomatic and reversible deficiency disease has been established for iron, iodine, copper, zinc, and selenium. Other elements, including chromium, manganese, molybdenum, and vanadium, have undoubted biological activity, but their relationship to clinical practice is not as clear.

Evidence for association of vitamins and health

Evidence for the association of vitamins with health forms three groups. At the first level, experimental observation shows that a nutritional derangement in metabolic function can be corrected in a person or animal by addition of a certain organic compound back into the diet. This evidence basically follows Koch's postulates. Early experimental research established the necessity of a number of vitamins, demonstrated their metabolic effect, and identified their sources in the diet. Diets defective in these organic compounds produce a defined syndrome and are clearly corrected when the vitamin is added back to the diet. Great improvements in worldwide health followed this basic nutritional discovery.

True vitamin deficiency states appear to be rare or infrequently diagnosed in Western medicine. Most of these deficiency states are associated with starvation. Clearly, replacement of the specific vitamin associated with vitamin-related disease results in a clinical cure. However, there is concern that subclinical deficiencies of vitamins might be associated with development of chronic disease even in the absence of overt symptoms and signs. Diagnosing these subclinical deficiencies has been problematic because it is difficult to measure vitamin levels. Measurement of vitamin levels usually requires high pressure liquid chromatography and is very expensive in clinical practice. Some surrogate markers are available, including retinol-binding protein, methylmalonic acid, and homocysteine levels. All measurements of vitamins are affected by the acute-phase reaction of hepatic proteins and chronic inflammatory disease.

The second level of evidence is epidemiological. By examining the dietary history of a population and noting the types of deranged metabolic functioning (disease), it might be possible to identify the components of a "healthy diet", even when the diet might contain not-yet-recognized compounds. These trials often use self-reported dietary intake or measurement of vitamin levels, either taken at some point prior to the development of a disease or after the disease has manifested.

This epidemiological research is intriguing and hypothesis-generating. However, epidemiological association cannot prove causality. These epidemiological reports produce a great deal of methodological problems. For example, daily intake of green-yellow vegetables has been associated with a 26% reduction in the risk of death from all strokes in men and women when compared with intake of once or less per week. Daily fruit intake has been associated with a 35% reduction in risk of all strokes in men and a 25% reduction in women. These data were based on a cohort study of 40 349 Japanese adults followed from 1980–1998 (Sauvaget et al 2003). The data on dietary intake was only recorded once in 1980. In other words, the amount of fruit and vegetables reported at one point in time predicts a decreased risk of stroke eighteen years later. We could conclude that a self-reported daily intake of vegetables or fruit may prevent stroke. It is also equally possible that people who eat fruit and vegetables differ in some unmeasured way from people who do not, and that this confounds the association.

The third, and most rigorous level of evidence, is a randomized, controlled clinical trial. The effect of a

hypothetical vital nutrient can then be directly observed over time in a population.

Epidemiological associations

A large body of epidemiological evidence suggests that eating a diet rich in sources of vitamins has a protective effect on development of disease. If disease can be prevented or delayed, longevity can be increased. Therefore, most people believe that they can ward off many if not most diseases and disability simply by knowing what foods to eat, what supplements to consume, and what leisure activities to pursue. This belief is encouraged by the emphasis on preventive medicine. Millions of people now eat low-fat, high-fiber diets, take antioxidant supplements, drink alcohol only in moderation, stay slim, and exercise.

Table 1 summarizes examples of the epidemiological associations of vitamins with specific disease states. The epidemiological data suggest a clear association between elevated homocysteine levels and higher risk of stroke and cardiovascular disease. The risk of stroke is also higher for persons who consume less fruits and vegetables. Folate levels, which are dependent on homocysteine levels, are also predictive of cardiovascular risk. Vitamin B6 has also been associated with cardiovascular risk and lipids.

Taken together, the association between homocysteine levels is strong. An association has been shown for carotid disease (5 studies), coronary disease (2 studies), peripheral vascular disease (1 study), and aortic atherosclerotic disease (1 study). An increased risk of cardiovascular disease and high levels of homocysteine levels has been shown in ten of thirteen case-control studies and one cohort study. A decreased risk for cardiovascular disease was also shown with high levels of folate (3 of 5 prospective and 1 of 2 retrospective studies) and vitamin B6 (2 of 2 prospective and 2 of 2 retrospective studies) but not with high levels of vitamin B12 (1 prospective and 2 retrospective studies) (Eikelboom et al 1999).

Other studies have not supported a link between supplemental vitamins and disease. The self-reported intake of vitamins E, C, or multivitamins was not associated with decreased incidence of cardiovascular disease or cardiovascular mortality after adjusting for known cardiovascular risk factors in a large observational study of male physicians (Muntwyler et al 2002).

Lung function studies illustrate the sometimes confusing data from epidemiological surveys. Forced expiratory volume was associated with intake of vitamin E in Finland, but only with dietary intake of fruit in Italy, and only with betacarotene intake in the Netherlands. In all three countries, men with above-average intakes of both fruit and vegetables had a higher forced expiratory volume than those with a low intake of both foods. After adjustment for energy intake, the association of all three antioxidants disappeared (Tabak et al 1999). Differences across populations, even over relatively small distances, confound these studies.

Micronutrient intake, including lutein, zeaxanthin, anhydrolutein, alphacryptoxanthin, betacryptoxanthin, lycopene, dihydrolycopene, alphacarotene, betacarotene, total carotenoids, retinol, alphatocopherol, betatocopherol, gammatocopherol, deltatocopherol, and total tocopherols, were examined in men who developed bladder cancer after 20 years of surveillance and compared with age-matched controls. There were statistically significant inverse linear trends in risk for alphacarotene, betacarotene, lutein plus zeaxanthin, betacryptoxanthin, and total carotenoids. However, after adjustment for pack-years of cigarette smoking none of the inverse trends remained significant (Nomura et al 2003).

Baseline intake of carotenes and vitamin C, or vitamin E, in supplemental or dietary (nonsupplemental) form or in both forms, was not related to a decreased risk of dementia of the Alzheimer type after 4 years of follow-up (Luchsinger et al 2003).

Not all observations demonstrate this effect. In one of the largest epidemiological observations, 71 910 female participants in the Nurses' Health Study and 37 725 male participants in the Health Professionals' Follow-Up Study who were free of major chronic disease were followed for incidence of cardiovascular disease, cancer, or death. A semiquantitative food-frequency questionnaire was obtained in 1984, 1986, 1990, and 1994 for women and in 1986, 1990, and 1994 for men. The outcome was analyzed in 1998. For men and women combined, persons who consumed the highest quintile of total fruit and vegetables did not have a lower risk for major chronic disease compared with those in the lowest quintile of consumption. Total fruit and vegetable intake was inversely associated with risk of cardiovascular disease, but not with overall cancer incidence. The benefits occurred in persons who had five or more daily servings. Of the food groups analyzed, green leafy vegetable intake showed the strongest inverse association with major chronic disease and cardiovascular disease. For an increment of one serving per day of green leafy vegetables, relative risks were 0.95 (95% confidence intervals [CI] = 0.92–0.99)

Table 1 Examples of epidemiological associations with diet, vitamins, or supplements with specific diseases

Study	Population	Condition	Association	Results	95% CI
Kittner et al 1999	167 women aged 15–44 years vs 328 women without a stroke	First ischemic stroke	Plasma homocysteine level ≥ 7.3 μmol/L	Odds ratio 1.6	1.1–2.5
Cancer Prevention Study 2000 – Hirvonen et al 2000	26 593 male smokers, aged 50–69 years	Cerebral infarction	Dietary intake of p-carotene	Relative risk 0.77	0.61–0.99
Cancer Prevention Study 2002 – Hirvonen et al 2000	26 593 male smokers, aged 50–69 years	Cerebral infarction	Lycopene, lutein, zeaxanthin, Vitamin C, flavonols, flavones, vitamin E	No association	
Robinson et al 1998	750 patients vs 800 controls	Coronary artery disease	Homocysteine concentrations > 80th percentile of control subjects	Increased risk	
Robinson et al 1998	750 patients vs 800 controls	Coronary artery disease	Red cell folate < 10th percentile of controls	Increased risk	
Robinson et al 1998	750 patients vs 800 controls	Coronary artery disease	Vitamin B6 < 20th percentile of controls	Increased risk	
Anderson et al 2000	1412 patients	Coronary artery disease	Plasma total homocysteine levels	Higher 3-year mortality	15.7% vs 9.6%
Muntwyler et al 2002	83 639 male US physicians with no history of cardiovascular disease (CVD) or cancer	Cardiovascular disease or cardiovascular mortality	Self-reported use of vitamins E, C, or multivitamins	No association	
Hung et al 2004	71 910 female participants in the Nurses' Health Study and 37 725 male participants in the Health Professionals' Follow-Up Study, free of chronic disease	Incidence of cardiovascular disease, cancer, or death	Total fruit and vegetable intake by dietary questionnaire	Relative risk for major chronic disease of 0.95 for highest quintile vs lowest. Relative risk for greater than 5 servings daily 0.88 for cardiovascular disease and 1.00 for cancer	0.89–1.01 for major chronic disease; 0.81–0.95 for cardiovascular disease; 0. 95–1.05 for cancer
Chen et al 2002	15 317 men and women > 20 years of age	Hypertension	Lower levels of vitamin A and vitamin E	Higher risk of hypertension	43% vs 18%
Chen et al 2002	15 317 men and women > 20 years of age	Hypertension	Higher levels of alphacarotene and betacarotene	Lower risk of hypertension	16% vs 11%
Chen et al 2002	15 317 men and women > 20 years of age	Hypertension	Higher levels of vitamin C	Lower diastolic pressure	
Tabak et al 1999	Finland (n = 1248), Italy (n = 1386), and the Netherlands (n = 691) middle-aged men	Pulmonary	Higher intake of fruits, vegetables	Higher forced vital capacity	53 mL–118 mL
Tabak et al 1999	Finland (n = 1248), Italy (n = 1386), and the Netherlands (n = 691) middle-aged men	Pulmonary	Higher intake of vitamin C, betacarotene	No association	
Tabak et al 1999	Finland (n = 1248), Italy (n = 1386), and the Netherlands (n = 691) middle-aged men	Pulmonary	Higher intake of vitamin E	No association	
Nomura et al 2003	9345 Japanese-American men	Bladder cancer	Alphacarotene, betacarotene, lutein plus zeaxanthin, betacryptoxanthin and total carotenoids	No association after adjusting for smoking	
Luchsinger et al 2003	980 elderly subjects free of dementia at baseline, followed for mean 4 years	Alzheimer disease	Carotenes and vitamin C, or vitamin E in supplemental or dietary (nonsupplemental) form or in both forms	No association	

for major chronic disease and 0.89 (95% CI = 0.83–0.96) for cardiovascular disease (Hung et al 2004). These findings suggest that high consumption of fruits and vegetables results in a small reduction in the risk of cardiovascular disease. There was no association found between fruit and vegetable intake (either total or of any particular group) and overall cancer incidence.

Randomized controlled trials

Unfortunately, randomized controlled trials of specific supplements have failed to demonstrate a consistent or significant effect of any single vitamin or combination of vitamins on incidence of or death from cardiovascular disease (Morris and Carson 2003). Vitamin E plus vitamin C plus betacarotene showed no difference in all-cause, vascular, or nonvascular mortality, or secondary measures including major coronary events, stroke, revascularization, and cancer compared with placebo (Heart Protection Study Collaborative Group 2002). In a meta-analysis of 135 967 participants in 19 randomized controlled trials using vitamin E, nine of eleven trials showed an increased risk for all-cause mortality at a dose greater than or equal to 400 IU per day of vitamin E. No increase in all-cause mortality was seen for doses less than 400 IU per day in these trials, but a dose-response analysis showed that a statistically significant relationship between vitamin E dosage and all-cause mortality began at a dose greater than 150 IU/day (Miller et al 2005). A similar increase in mortality has been described in very high dose vitamin E (2000 IU per day) supplementation in persons with Alzheimer dementia (Sano et al 1997; Miller et al 2005).

Four placebo-controlled trials have not shown a benefit of betacarotene, alone or combination with alphatocopherol or retinol, or alphatocopherol alone on the development of lung cancer. For people with risk factors for lung cancer, no reduction in lung cancer incidence or mortality was found in those taking vitamins alone compared with placebo. For people with no known risk factors of lung cancer, none of the vitamins or their combinations appeared to have any effect. In fact, in combination with retinol, a statistically significant increase in risk of lung cancer incidence was found compared with placebo (Caraballoso et al 2003).

Table 2 summarizes examples of randomized controlled trials and meta-analytical reviews for vitamins and specific diseases. The data from randomized controlled trials show (with a few exceptions) that supplementation with vitamins has not had much effect on disease states. Vitamin D supplementation, along with calcium, has been demonstrated to reduce hip fracture rate in older persons. The use of mineral and vitamin supplements has been shown to slow the progression of, but not prevent, age-related macular degeneration. Folate may have some role in the treatment of depression, although the trials have been small in numbers. Vitamin C may, or may not, have an effect on hypertension, but the longest trials were only two months in duration. Six controlled trials on supplementation of vitamin C in persons with asthma showed no appreciable benefit on asthma outcome (Ram et al 2003).

Trace elements, but not vitamins alone, have been shown to produce higher antibody titers after influenza vaccination in older persons, but had no effect on infection rate or survival. In a meta-analysis of 8 trials of older persons, the effect on multivitamin and mineral supplements on infectious disease was examined. Multivitamins and mineral supplements were found to reduce the mean annual number of days spent with infection by 17.5 in three studies. However, the odds ratio for having at least one infection in the study period and the incidence rate for treated compared with control subjects was not different (El-Kadiki and Sutton 2005).

Summary and clinical relevance

Evidence of epidemiological associations of vitamins and disease states has been found for nine vitamins. Inadequate folate status is associated with neural tube defect and some cancers. Folate and vitamins B6 and B12 are required for homocysteine metabolism and are associated with coronary heart disease risk. Vitamin E and lycopene may decrease the risk of prostate cancer. Vitamin D is associated with decreased occurrence of fractures when taken with calcium (Fairfield and Fletcher 2002). Zinc, betacarotene, and vitamin E appear to slow the progression of macular degeneration, but do not reduce the incidence.

In observational studies (case-control or cohort design), people with high intake of antioxidant vitamins by regular diet or as food supplements generally have a lower risk of myocardial infarction and stroke than people who are low-consumers of antioxidant vitamins. The association in observation studies has been shown for carotene, ascorbic acid, and tocopherol. The use of various dietary supplements, including vitamins, to prevent or delay disease or aging rests for the most part on epidemiological associations. It does appear from this data that a diet rich in vitamins is associated with a tendency to improved health.

However, the results from controlled trials are dismal. In randomized controlled trials, antioxidant vitamins as food

Table 2 Examples of controlled trials of vitamins or supplements on specific diseases

Study	Population	Condition	Intervention	Results	Effect
Heart Protection Study Collaborative Group 2002	20 536 subjects followed 5 years	Coronary heart disease, vascular occlusive disease, diabetes mellitus, hypertension	Vitamin E 600 mg/d, plus vitamin C 250 mg/d, plus betacarotene 20 mg/d or placebo	All-cause, vascular, or nonvascular mortality, or secondary measures including major coronary events, stroke, revascularization, and cancer	No difference
The SU.VI.MAX Study 2004 – Hercberg et al 2004	13 017 persons, age 45–60, followed 7.5 years	Cancer, cardiovascular disease or cardiovascular mortality	120 mg ascorbic acid, 30 mg of vitamin E, 6 mg of betacarotene, 100 µg of selenium, 20 mg of zinc vs placebo	Total cancer incidence 4.1% vs 4.5%; ischemic cardio-vascular disease incidence 2.1% vs 2.1%, all-cause mortality 1.2% vs 1.5%	No difference; may have small protective effect in men
HOPE and HOPE-TOO Trial 2005	3994 persons, > 55 years with CVD or cardiovascular disease; diabetes mellitus followed 7 years	Cardiovascular events and cancer	Vitamin E 400 IU/d vs placebo	Cancer incidence 11.6% vs 12.3%; cancer deaths 3.3% vs 3.7%; major cardiovascular events 21.5% vs 20.6%	No difference. Higher risk of congestive heart failure (CHF) and hospitalization for CHF
Heart Protection Study Collaborative Group 2002	15 000 men aged 40–80, followed 5 years	Cardiovascular disease	Daily combination of vitamin E (600 mg), vitamin C (250 mg), and betacarotene (20 mg)	Incidence	No significant reduction
Meta-analysis 2005 – Miller et al 2005	135 967 participants in 19 clinical trials	All-cause mortality	Vitamin E ≥ 400 IU/d	39 deaths per 10 000 persons (3–74 per 10 000 persons; p = 0.035)	Higher mortality
Mullan et al 2002	30 patients, 45–70 years old, with type 2 diabetes, followed 4 weeks	Hypertension	500 mg of ascorbic acid daily	Mean systolic 9.9 mmHg, mean diastolic 6.0 mmHg	Reduced systolic blood pressure
Kim et al 2002	439 subjects followed 5 years	Hypertension	500 mg of vitamin C daily	Blood pressure	No reduction
Pfeifer et al 2001	148 women, mean age 74 years followed 8 weeks	Hypertension	1200 mg calcium plus 800 IU vitamin D3 or 1200 mg calcium/day	Decrease in systolic blood pressure of 9.3%	Improved
Ram et al 2003	Six trials	Asthma	Vitamin C supplementation	Asthma outcome	No difference
Caraballoso et al 2003	109 394 subjects	Lung cancer	Betacarotene, alone or combination with alpha-tocopherol or retinol, or alphatocopherol alone	Cancer incidence	No reduction
The Betacarotene and Retinol Efficacy Trial 1996 – Omenn et al 1996	18 314 subjects, 45–74 years, at high risk, followed 4 years	Lung cancer	Betacarotene and retinyl palmitate compared with placebo	28% (4%–57%) higher cancer incidence and 17% (3%–33%) higher total mortality in the supplemented group	Worse outcome
Virtamo et al 2003	25 390 persons followed 6 years	Prostate cancer	Alphatocopherol	Relative risk 0.88 (0.76–1.03)	No difference
Virtamo et al 2003	25 390 persons followed 6 years	Prostate cancer	Betacarotene	Relative risk 1.06 (0.91–1.23)	No difference
Greenberg et al 1994	864 subjects	Incidence of colon polyps	Placebo, betacarotene (25 mg daily), vitamin C (1 g daily) and vitamin E (400 mg daily), or betacarotene plus vitamins C and E	Relative risk 1.01 (0.85–1.20) for betacarotene and 1.08 (0.91 to 1.29) for vitamin C and E	No difference
Rodriguez-Martin et al 2003	50 subjects, followed 1 year	Alzheimer dementia	Thiamine supplementation	Cognitive status	No benefit

continued

Study	Population	Condition	Intervention	Results	Effect
Alzheimer's Disease Cooperative Study 1997 – Sano et al 1997	341 subjects followed 2 years	Alzheimer dementia	Vitamin E 1000 mg twice a day, selegiline 5 mg twice a day, both or placebo	Time to either death, institutionalization, decline in activities of daily living, or progression to severe dementia	Reduced in vitamin E group (670 days) and selegiline group (655 days) compared with placebo group (440 days), higher mortality 1.08 (1.01–1.14)
Lerner et al 2002	15 subjects	Schizophrenia	Vitamin B6 400 mg vs placebo	Mental status	No difference
Taylor et al 2003	247 subjects	Depression	Folic acid	Reduction in depression scores	2.65 points, CI 0.38–4.93
Christen et al 2003	22071 male US physicians aged 40–84 years, followed 1 year	Cataract	Betacarotene 50 mg on alternate days vs placebo	Incidence	No benefit
Evans 2003	4119 subjects in 7 trials	Age-related macular degeneration, progression to advanced disease	Antioxidant and zinc supplementation	Risk ratio 0.72 (0.52–0.98)	Less risk
Evans 2003	4119 subjects in 7 trials	Age-related macular degeneration	Vitamin E, betacarotene or both	Prevention	No benefit
Girodon et al 1999	725 institutionalized elderly subjects > 65 years, followed 2 years	Antibody titers, respiratory infections, urinary tract infections, survival rate	Trace elements (zinc and selenium sulfide) or vitamins (betacarotene, ascorbic acid, and vitamin E) or a placebo	Antibody titers after influenza vaccine were higher in groups that received trace elements alone or associated with vitamins, but the vitamin group had significantly lower antibody titers	Higher titers with minerals but low with vitamins
Chandra 1992	96 subjects	Infection-related illness, days taking antibiotics, nutritional deficiencies	Vitamin A 400 units, betacarotene 16 mg; thiamine 2.2 mg; riboflavin 1.5 mg; niacin 16 mg; vitamin B6 3.0 mg; folate 400 µg; vitamin B12 4.0 µg; vitamin C 80 mg; vitamin D 4 µg; vitamin E 44 mg; iron 16 mg; zinc 14 mg; copper 1.4 mg; selenium 20 µg; iodine 0.2 mg; calcium 200 mg; and magnesium 100 mg vs placebo (calcium, 200 mg, and magnesium, 100 mg)	23 (23–28) vs 48 fewer infection-related illness days; 18 (12–16) vs 32 fewer days taking antibiotics	Improved
El-Kadiki et al 2005	8 trials in older adults	Days with infection, at least one infection, incident infections	Any combination of vitamin or mineral supplements	14 (10–18) fewer days with infection; at least one infection 1.10 (0.81–1.50); incident infections 0.89 (0.78–1.03)	Fewer days with infection, no difference in incident infections
Gillespie et al 2003	Frail elderly subjects	Hip fracture and vertebral fracture incidence	Vitamin D3 supplementation along with calcium	Risk ratio 0.74 (0.60–0.91)	Less risk
Gillespie et al 2003	Frail elderly subjects	Hip fracture and vertebral fracture incidence	Vitamin D3 supplementation alone without calcium	Risk ratio 1.20 (0.83–1.75)	No difference
Gillespie et al 2003	In healthy younger, ambulatory subjects	Hip fracture	Vitamin D3 supplementation along with calcium	Risk ratio 0.36 (0.01–8.78)	No difference
Gillespie et al 2003	In healthy younger, ambulatory subjects	Nonvertebral fracture	Vitamin D3 supplementation along with calcium	Risk ratio 0.46 (0.23–0.90)	Less risk

supplements have no beneficial effects in the primary prevention of myocardial infarction and stroke. The apparent beneficial results of a high intake of antioxidant vitamins reported in observational studies have not been confirmed in large randomized trials (Asplund 2002).

The discrepancy between different types of studies is probably explained by the fact that dietary composition and supplement use is a component of a cluster of healthy behavior. An alternative hypothesis is that there are as yet unknown essential organic compounds in certain foods.

Much of the enthusiasm for the use of vitamin or mineral supplements to prevent disease or increase longevity results from the belief that supplementation is harmless. However, serious adverse events have been reported. Toxicity may result from excessive doses of vitamin A during early pregnancy and from other fat-soluble vitamins taken in high doses. There is increasing concern from randomized, controlled trials that betacarotene and vitamin E may be associated with a higher mortality risk.

The most prudent approach is to recommend a daily intake of fruits and vegetables as a likely source of essential nutrients. Failing compliance with a natural source of essential nutrients, and in populations at high risk of vitamin deficiency, vitamin supplements should be encouraged. Vitamin supplements should be used as replacement doses guided by RDI and supertherapeutic doses should be avoided.

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