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Rationale for Use of Vitamin and Mineral Supplements

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Introduction

Current research indicates that health benefits which go beyond the repletion of potential deficiency states can be derived from vitamins and minerals. In most instances, these benefits may be conveyed by intakes either at or above recommended daily allowances. For some of these health benefits the scientific evidence base is convincing, while for others, support for potential benefits is just emerging. In many cases the association between a particular vitamin or mineral and its beneficial effect is derived from nutritional epidemiological studies. Intervention studies are needed in many promising areas in order to demonstrate a conclusive nutrient-benefit link. Additionally, in the case of multivitamin supplementation, further investigation is needed in order to determine and characterize the nutrient or nutrient interactions which produce a particular beneficial effect. What follows describes the emerging benefits of vitamins and minerals, and the scientific support for each.

As the increasing importance of nutrients and their health benefits become known, various health agencies and organizations have recognized the need to issue recommendations for vitamin and mineral supplementation and/or fortification of food. These include the U.S. Public Health Department, Centers for Disease Control, Department of Health and Human Services, the National Osteoporosis Foundation, and many international health organizations and boards of health.

Vitamin A

Dietary antioxidants, including carotenoids and vitamin A, are hypothesized to decrease the risk of age-related cataracts by preventing oxidation of proteins or lipids within the lens.[1,2] Information on the role of vitamins in eye disease is discussed in Section 62.

Vitamin A deficiency appears to be common in individuals with HIV infection. Low levels of vitamin A are associated with greater disease severity.[3,4] Transmission of the virus

TABLE 65.1

Vitamin A — Established Benefits

Important for normal growth in children
Necessary for wound repair
Involved in RNA synthesis
Helps to form and maintain healthy skin, eyes, teeth, gums, hair, mucous membrane, and various glands
Involved in fat metabolism
Important for resisting infectious diseases
Necessary for night and color vision

TABLE 65.2

Vitamin A — Emerging Benefits

Use	Findings	Reference
Age-related cataracts	Vitamin A use not related to decreased risk of cataract	2
HIV	High doses may be protective	3, 4, 5
Measles	High doses decrease morbidity and mortality	6, 7
Acne	High doses may be helpful	8
Crohn's disease	Variable response to high doses	9, 10, 11

from a pregnant mother deficient in vitamin A to her infant has been reported.[5] However, there have been no intervention studies to determine whether vitamin A supplementation is helpful.

The potential benefit of vitamin A therapy for measles was first reported in 1932,[6] and a recent study in South African children under 13 years of age showed that large doses (400,000 IU) of vitamin A resulted in lower complication rates and mortality. Low vitamin A levels have been noted in young children with measles, and are associated with the highest mortality.[7] WHO, UNICEF, and the American Academy of Pediatrics recommend that children with measles be examined for vitamin A deficiency.

Large quantities of analogs of vitamin A, on the order of 300,000 IU per day for females and 400 to 500,000 IU per day for males, have been used successfully to treat a severe type of acne known as cystic acne.[8] However, such high doses of vitamin A are potentially toxic, and topical retinol therapy is more appropriate.

Vitamin A is needed for the growth and repair of cells that line both the small and large intestines. Over the years, reports have appeared of individuals with Crohn's disease responding to vitamin A therapy at a dose of 50,000 IU per day.[9,10,11] See Tables 65.1 and 65.2 for the established and emerging benefits of vitamin A.

Beta-Carotene

Based on the unanimous recommendation by health professionals that diets rich in fruits and vegetables may help reduce the risk of cancer and heart disease, scientists have started to identify the components in these foods which are responsible for the health benefits. Because beta-carotene is one of the more abundant carotenoids in fruits and vegetables, it dominated the research on carotenoids in the 1980s following the report published in *Nature* by Dr. Richard Peto et al., entitled "Can dietary beta-carotene materially reduce cancer rates."[12] See Table 65.3 for the established benefits of beta-carotene.

TABLE 65.3

Beta-Carotene — Established Benefits

Supplies vitamin A
Antioxidant function
Supports the immune system

TABLE 65.4

Important Beta-Carotene Cancer Trials

Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study[14] (ATBC Study) — also called the Finnish study	29,133 male smokers, 50-69 years of age	50 mg vitamin E 20 mg beta-carotene or both for 5-8 years	No evidence of prevention of lung and other cancers. Beta-carotene group had a 16% greater incidence of lung cancer in smokers
Beta-Carotene and Retinol Efficacy Trial[15] (CARET)	18,314 men and women smokers and former smokers	25,000 IU vitamin A 30 mg beta-carotene	Increase of 28% in lung cancer and 17% in cancer mortality
Physicians' Health Study[16] (PHS)	22,071 males, mainly non-smokers	50 mg beta-carotene every other day for 12 years	No effect on cancer rates for prostate, bowel or lung or for overall incidence of cancer or mortality

In addition to extensive epidemiological data, beta-carotene showed strong promise in laboratory studies with cancer cells and animals (see Albanes and Hartman, *Antioxidants and Cancer,*[13] for the long list of epidemiological studies). The results of three major double-blind, randomized, placebo-controlled clinical studies, however, were surprising (see Table 65.4).

The conclusions demonstrating a potentially adverse effect of beta-carotene in smokers were questioned because of the evidence from epidemiological and basic biochemical studies whose results were contrary. It has been suggested that the very high doses of beta-carotene used in the above studies might have interfered with the absorption of carotenoids other than beta-carotene.

Several ongoing intervention studies may help clarify the inconsistency of these findings. The Chinese Cancer Prevention Study[17] evaluated beta-carotene (15 mg), vitamin E (30 mg), and selenium (50 μg) and found a non-significant 10% decrease in cerebrovascular mortality in a group receiving treatment compared to that of an untreated group. There was a 13% reduction of borderline significance in total cancer mortality in the treated group and a 21% reduction in gastric cancer, which was significant. Because beta-carotene was evaluated in combination with other nutrients, it is not possible to isolate the effect attributable to beta-carotene alone. Other nutrients may have had an effect in the poorly nourished group included as study subjects, and results may not be applicable to well-nourished individuals.

Several smaller studies of beta-carotene and premalignant lesions have shown interesting preliminary results. A 66% reduction in the frequency of pre-malignant buccal micronuclei was observed after supplementation of 26 mg of beta-carotene for nine weeks.[18] A 71% reduction was observed in patients with oral leukoplakia after a six-month intake of 30 mg per day of beta-carotene.[19]

Apart from cancer prevention, beta-carotene has been studied for its effect in coronary heart disease and cataract. A subgroup of the Physicians' Health Study (PHS) which included 333 physicians with unstable angina or a prior coronary revascularization pro-

TABLE 65.5

Beta-Carotene — Emerging Benefits

Cancer — lung, cervix, oral, colorectal, pancreas, prostate
Cardiovascular disease
Cataracts
Restenosis after angioplasty

TABLE 65.6

Important Beta-Carotene Cardiovascular Trials

Agent	Highest Daily Intake Quintile	Lowest Daily Intake Quintile	Relative Risk	P Value
Nurses Health Study[21] *Antioxidant Vitamins and Risk of Coronary Heart Disease*				
Beta-carotene	>1404 IU	<3850 IU	0.78	.02
Vitamin E	>21.6 mg	<3.5 mg	0.66	<.001
Vitamin C	>359 mg	<93 mg	0.80	.15
Health Professionals Follow-up Study[22] *Antioxidant Vitamin Intake and Risk of Coronary Heart Disease*				
Beta-carotene			0.71	.03
Vitamin E			0.60	.01
Vitamin C			1.25	.98
Massachusetts Elderly Cohort Study[23] *Beta-Carotene Intake and Risk of Cardiovascular Disease*				
Endpoint				
CVD death			0.57	.02
Fatal MI			0.32	.02

cedure had a 20 to 30% reduction in vascular disease. High dietary intakes of beta-carotene were found to be associated with a decreased risk of myocardial infarction in the Rotterdam study, which investigated the dietary intakes of 4802 elderly men and women over the course of four years.[20] A similar effect was not seen for either vitamin C or E. See Table 65.5 for emerging benefits of beta-carotene. The results of several additional important prospective studies are included in Table 65.6.

People with low blood levels of antioxidants and those who eat few antioxidant-rich fruits and vegetables are at high risk for cataracts.[24,25] See information in Section 62 on eye disease.

Lycopene is an antioxidant carotenoid found commonly in tomatoes. Although not a vitamin per se, nor a provitamin (for vitamin A), specific benefits of lycopene are beginning to be elucidated, particularly with respect to certain cancers. Of particular note is an observational finding that high intakes of lycopene are associated with lower rates of prostate cancer. An excellent overview by Giovannucci[26] covers lycopene and the epidemiological evidence supporting its currently known health benefits.

In conclusion, basic metabolic research as well as animal and epidemiological studies all suggest major benefits from carotenoids. These benefits, however, have yet to be confirmed in double-blind intervention studies.

TABLE 65.7

Riboflavin — Established Benefits

Essential for building and maintaining body tissues
Necessary for healthy skin
Prevents sensitivity of the eyes to light
Necessary for protein, fat, and carbohydrate metabolism
Important for the proper function of the nervous system

TABLE 65.8

Riboflavin — Emerging Benefits

Use	Findings	Reference
Age-related cataract	Riboflavin deficiency associated with higher incidence of cataract	27-30
Exercise	Aerobic exercise may deplete riboflavin Supplementation with riboflavin does not appear to increase performance	31-34
Pregnancy and exercise	Riboflavin may be helpful	35
Migraine	High doses in a limited trial produced beneficial results	36

Riboflavin

Deficiency of riboflavin, a precursor of flavin adenine dinucleotide, has been believed by some to be associated with cataract formation,[27,28] Lenticular reduced glutathione, diminished in all forms of human cataract, requires flavin adenine dinucleotide as a coenzyme for glutathione reductase. Despite this putative connection with riboflavin, clinical results of studies in this area are equivocal, and the degree of riboflavin deficiency encountered in the general population would not be considered to be cataractogenic. Clinically, lower intakes of riboflavin are not found to be a risk factor for cataract.[29,30] See Section 62 on eye disease for further discussion of this topic.

Review of riboflavin requirements associated with exercise in several different study groups yields equivocal results. Aerobic exercise may deplete riboflavin as well as other B-vitamins.[31] However, riboflavin status, assessed using erythrocyte glutathione reductase activity coefficient, shows that while riboflavin requirements of women increase with exercise training, additional riboflavin intake does not enhance or result in improvements in endurance.[32,33] Additionally, riboflavin depletion is not related to the rate or composition of weight loss in overweight women.[34] Interestingly, in a cohort of pregnant women who exercised and took vitamin-mineral supplements, participation in a walking program slightly improved aerobic capacity without affecting riboflavin or thiamin status.[35]

Minimal data are available from one study of high doses (400 mg per day) of riboflavin that successfully treated migraine patients.[36] Further work in this area is needed. See Tables 65.7 and 65.8 for established and emerging benefits of riboflavin.

Niacin

The body uses niacin in the process of releasing energy from carbohydrates, to form fat from carbohydrates, and to metabolize alcohol. Niacin comes in two basic forms: niacin

TABLE 65.9

Niacin — Established Benefits

Helps prevent pellagra
Helps cells release energy from food
Aids the nervous system
Helps prevent loss of appetite

TABLE 65.10

Niacin — Emerging Benefits

Use	Findings	Reference
Hypercholesterolemia	Lowers elevated cholesterol levels	37-40
Hypertriglyceridemia	Lowers elevated triacylglcerol levels	37

(also called nicotinic acid) and niacinamide (also called nicotinamide). High levels of niacin — usually several grams per day — lower cholesterol, triglyceride, and triacylglycerol levels and raise HDL cholesterol levels.[37] The niacinamide form, commonly found in multivitamin preparations, does not decrease elevated cholesterol. See Tables 65.9 and 65.10 for established and emerging benefits of niacin.

A variation of niacin, called inositol hexaniacinate, has also been used and has not been linked with the flushing seen with high doses of niacin. It is sometimes prescribed by physicians in Europe to help lower cholesterol. Dosages used are 500 to 1000 mg taken three times per day.[38,39] This form of niacin lowers serum cholesterol but appears to have fewer side effects.[40]

Vitamin B_6

Vitamin B_6 has a significant role to play, along with folate and vitamin B_{12}, in the reduction of elevated homocysteine levels associated with increased risk of cardiovascular disease — specifically, coronary artery disease and stroke. This topic is covered in the section on folate.

Vitamin B_6 also plays a significant role in the immune function of the elderly. *In vitro* indices of cell-mediated immunity in healthy elderly adults indicate that deficiency of vitamin B_6 is associated with impairment of immune function. This impairment appears to be reversible with vitamin B_6 repletion.[41] The levels of vitamin B_6 absorption, phosphorylation, and excretion appear not to be affected by age.[42]

Vitamin B_6 has been shown to reduce the effects of estrogen in animals. Since excess estrogen may be responsible in part for premenstrual symptoms (PMS), a number of studies in humans have demonstrated that 200 to 400 mg of vitamin B_6 per day for several months can relieve symptoms of PMS.[42-46] In other studies, however, the amount of vitamin B_6 used may be too low,[47] or the length of the trial too short,[48] and other studies have not found vitamin B_6 helpful.[49,50]

Many diabetics have low blood levels of vitamin B_6.[51,52] Levels of vitamin B_6 are even lower in diabetics with nerve damage.[53] Vitamin B_6 supplements has been demonstrated to improve glucose tolerance in women with diabetes associated with pregnancy.[54,55] Vitamin B_6 is also partially effective for glucose intolerance induced by birth control pills.[56] For some individuals with diabetes, a form of vitamin B_6 — pyridoxine alpha-ketoglutarate — improves glucose tolerance dramatically.[57] Vitamin B_6 (cyanocobalamin) has been found to help in some,[58] but not all, studies.[59]

TABLE 65.11

Vitamin B_6 — Established Benefits

Important in protein absorption and metabolism
Necessary for red blood cell formation
Necessary for the proper function of the nervous and immune systems
Helps maintain healthy teeth and gums
Needed for serotonin and melatonin production

TABLE 65.12

Vitamin B_6 — Emerging Benefits

Use	Findings	Reference
Immune function	Improves immune function in the elderly	41, 42
Premenstrual symptoms	High doses administered long-term may be helpful	43-50
Diabetes	Low levels are associated with diabetes	51-59
Carpal tunnel syndrome	Inconsistent results	60-68
HIV	Deficiency frequently found and associated with decreased immune function	69

It appears that many people with carpal tunnel syndrome (CTS) have vitamin B_6 deficiencies.[60] Some studies show that people with CTS are helped when given 100 mg of vitamin B_6 three times per day.[61,62] Although a few researchers have found benefits with lesser amounts,[63,64,65] the results have not been consistent.[66,67,68]

Lastly, it is worth noting that vitamin B_6 deficiency was found in more than one-third of HIV-positive men, and a deficiency of this vitamin is associated with decreased immune function.[69] See Tables 65.11 and 65.12 for established and emerging benefits of vitamin B_6.

Vitamin B_{12}

Higher blood levels of vitamins B_6, B_{12}, and folic acid are associated with low levels of homocysteine,[70] and supplementing with these vitamins helps to lower homocysteine levels.[71,72] Preliminary evidence indicates that vitamin B_{12} may be beneficial when included in supplements or in a food-fortification regimen together with folic acid. This topic is discussed further in the section on folate.

The addition of vitamin B_{12} enhances the homocysteine-lowering potential of a folic acid supplement. In one study, female volunteers were given folic acid alone or folic acid combined with one of two supplements containing different doses of vitamin B_{12}. Significant reductions in plasma homocysteine were observed in all groups receiving vitamin treatment. The combination of folic acid 400 µg plus 400 µg of vitamin B_{12} resulted in an 18% decrease in homocysteine levels. This was significantly larger than that obtained with a supplement containing folic acid alone (homocysteine decrease of 11%). Folic acid in combination with a low vitamin B_{12} dose (6 µg) affected homocysteine as well (decrease of 15%). These results suggest that the addition of vitamin B_{12} to folic acid supplements or enriched foods helps maximize the reduction of homocysteine and may thus increase the benefits achieved with the use of folic acid in the prevention of vascular disease.[73]

Lastly, vitamin B_{12} has a role in preventing vitamin B_{12} deficiency in the presence of folate use, especially in light of the increased fortification of foods with folic acid. (See rationale by Oakley.[74]) See Tables 65.13 and 65.14 for established and emerging benefits of vitamin B_{12}.

TABLE 65.13

Vitamin B_{12} — Established Benefits

Necessary for DNA synthesis
Helps prevent pernicious anemia
Helps to form red blood cells
Enhances utilization of nickel

TABLE 65.14

Vitamin B_{12} — Emerging Benefits

Use	Findings	Reference
Hyperhomocysteinemia	Alone and together with folate reduces homocysteine levels	70-73
Folate-induced vitamin B_{12} deficiency	Administration helps unmask vitamin B_{12} deficiency associated with folate use	74

Folic Acid

For the last 40 years, folic acid has almost exclusively been used to treat megaloblastic macrocytic anemia. There is now significant evidence that folate deficiency is associated with increased risk of several diseases. The most convincing is the association of folic acid deficiency with neural tube defects (NTDs) such as spina bifida and anencephaly, a predisposition to occlusive vascular disease associated with hyperhomocysteinemia, and several neoplastic or preneoplastic diseases. In addition, preliminary evidence suggests some association of folate deficiency with neuropsychiatric diseases.

Studies on folate and NTDs were conducted by the British Medical Research Council in 1991.[75] These demonstrated that high-dose folic acid supplements (4.0 mg per day) used by women who had a prior NTD-affected pregnancy reduced the risk of having a subsequent NTD-affected pregnancy by 70%. A conclusive trial conducted in Hungary showed that a multivitamin containing 0.8 mg folic acid protected against a first occurrence of NTD.[76]

In 1992 the Centers for Disease Control in the U.S. issued a recommendation that all women of childbearing age who are capable of becoming pregnant should consume 0.4 mg of folic acid per day to help prevent NTDs.[77] The U.K. Expert Advisory Group and other countries in Europe made similar recommendations.[78] The U.S. Food and Drug Administration has recently authorized a health claim on food labels and dietary supplements that folic acid contained in these products may help reduce the risk of NTD.[79] This is the only health claim currently permitted for a vitamin in the U.S.

A large body of evidence reveals that elevated blood homocysteine is a risk factor for cardiovascular disease, including atherosclerotic coronary heart disease and thromboembolic stroke. There is abundant evidence that folate deficiency and/or a genetic defect in the enzymes involved in homocysteine metabolism give rise to hyperhomocysteinemia. In addition to folate deficiency, vitamin B_6 and B_{12} deficiency has also been associated with elevated homocysteine levels. Patients with higher blood levels of these vitamins are at lower risk for occlusive vascular disease.[80]

Many studies show that folic acid alone or in combination with vitamins B_6 and B_{12} can reduce blood homocysteine levels.[81-90] Observational studies have shown that people who

consume multivitamins and/or cereal fortified with folic acid also have reduced homocysteine levels.[91-95] Levels of supplemental folic acid as low as 0.4 mg appear to be effective. A meta-analysis of 12 randomized trials confirms that folic acid has the dominant blood homocysteine-lowering effect.[90] The fortification of enriched grain with folic acid has been shown to increase folate plasma levels and decrease homocysteine levels in middle-aged and older adults.[94] While folic acid fortification was undertaken primarily to reduce the risk of NTDs, it may also have a beneficial effect on vascular disease.

Based on a meta-analysis of 27 studies relating homocysteine to vascular disease and 11 studies of folic acid effects on homocysteine levels, Boushey and Beresford[81] concluded that an increase of 350 μg/day of folate intake by men and 280 μg/day increase by women could potentially prevent 30,500 and 19,000 vascular deaths annually in men and women, respectively. Recent reports show that a small percentage of children, with or without a positive family history of cardiovascular disease,[96-98] have elevated homocysteine levels. Hyperhomocysteinemia may also be a risk factor for ischemic stroke in children. The data on children suggest that tracking of homocysteine levels from childhood on may be helpful in the planning and evaluation of future initiatives aimed at the prevention of cardiovascular disease.

While it has been shown that higher intake of folate may reduce homocysteine levels and that lower homocysteine levels are associated with reduced cardiovascular mortality, clinical intervention trials are needed to prove unequivocally that higher intakes of folate will help reduce the risk of cardiovascular disease. An excellent review of prospective cohort and case-control studies as well as cross-sectional and retrospective case-control studies concerning the association between homocysteine and cardiovascular risk has recently been published by Hankey and Eikelboom.[99]

In a preliminary report, a vitamin mixture of 2.5 mg of folic acid, 25 mg vitamin B_6, and 250 μg vitamin B_{12} stopped the progression of carotid plaques; some regression was also observed.[100] Excellent detailed reviews on homocysteine and vascular disease have been published.[101-105]

Several reports suggest an increased risk of colon, tracheobronchial tree, and cervical cancer, and preneoplastic dysplasia associated with folate deficiency.[106,107] Supplemental folic acid has been shown to partially reverse some cervical dysplasia.[106,108] In some instances, poor folate status may not by itself be carcinogenic, but it may predispose to the carcinogenicity of other agents.[109,110]

Lashner and Heidenreich[110] reported that the rate of colon cancer was 62% lower in patients with ulcerative colitis who were supplemented with folic acid. Giovannucci and Stampfer[111] examined the relationship between the intake of folate, both from supplements and food, and the risk for colon cancer in women in the Nurses Health Study. The results indicate that the use of multivitamin supplements for 15 or more years may decrease the risk for colon cancer by about 75%. The data are consistent with the hypothesis that folate intake is the principal nutritional factor associated with risk reduction. These findings support several recent studies, including the Health Professional Follow-Up Study, which have found a higher risk for colon cancer among persons with low folate. In the Giovannucci report, the association between colon cancer and folate was stronger with supplemental than with dietary folate. This is probably due to the fact that food folate is less bioavailable that supplemental folate. More recently, Zhang and Hunter[112] reported that the excess risk of breast cancer associated with moderate alcohol consumption may be reduced by folate. Alcohol is a known folate antagonist, and this could increase the requirement for folate.

Blount et al.[113] presented data on the possible mechanism by which folate deficiency enhances cancer risk. Folate deficiency results in abnormal DNA synthesis due to misin-

TABLE 65.15

Folic Acid — Established Benefits

Necessary for DNA synthesis
Important for cell formation
Prevents certain types of anemias
Helps maintain the function of the intestinal tract

TABLE 65.16

Folic Acid — Emerging Benefits

Use	Findings	Reference
Neural tube defects	0.4 mg per day prevents neural tube defects	75 -79
Hyperhomocysteinemia	Lowers homocysteine levels	80-104
Cancer	Deficiency is associated with an increased risk of colon, lung, cervical cancer	105-112
Cognitive function	Low levels are associated with Alzheimer's disease	113-115

corporation of uracil into DNA, leading to chromosome breakage. This breakage contributes to the risk of colon cancer.

Data to help elucidate the role of folate in Alzheimer's disease and depression are sparse and just emerging. Low blood levels of folate and vitamin B_{12} are often found in individuals with Alzheimer's disease.[114] The role of elevated homocysteine levels has been reported and needs to be expanded further.[115] Low folate blood levels may be associated with the weaker responses of depressed patients to antidepressants.[116] Factors contributing to low serum levels among depressed patients, as well as the circumstances under which folate may have a role in antidepressant therapy, must be further clarified. See Tables 65.15 and 65.16 for the established and emerging benefits of folate.

Vitamin C

Vitamin C has many functions in the body, including serving as an antioxidant and as a cofactor for several enzymes involved with biosynthesis.[117] The relationship between vitamin C and total serum cholesterol has been investigated in several studies.[118-123] In one intervention study, consumption of 1000 mg of vitamin C per day for four weeks resulted in a reduction in total serum cholesterol.[120] In another study, supplementation with 60 mg per day for two weeks had no effect.[118] Two observational studies found an inverse relationship between vitamin C status and total serum cholesterol concentrations.[122,123]

Low concentrations of plasma vitamin C have been associated with hypertension.[122,124-127] Several studies have reported beneficial effects of the administration of high doses of vitamin C on vasodilation.[128-131] One study found a 128% increase in brachial artery dilation in coronary artery disease patients, while a second found a nonsignificant increase of 27% in chronic heart failure patients.[131] Infusion of 10 mg of vitamin C per minute was observed to effect a 100% reversal of epicardial artery vasoconstriction in coronary spastic angina patients.[132]

Vitamin C may protect against cancer through several mechanisms, including inhibition of DNA oxidation. One potential mechanism is chemoprotection against mutagenic compounds such as nitrosamines.[133,134] In addition, vitamin C may reduce carcinogenesis through stimulation of the immune system, via a beneficial effect on phagocyte functions,

TABLE 65.17

Vitamin C — Established Benefits

Prevents scurvy
Maintains health of teeth, gums, and blood vessels
Necessary for wound repair
Important for collagen formation
Enhances iron absorption

such as chemotaxis,[135-138] or on the activity of natural killer cells and the proliferation of lymphocytes.[139-141] See Table 65.17 for the established benefits of vitamin C.

Table 65.18 (adapted from Carr[142]) lists prospective cohort studies of vitamin C intake associated with reduced cardiovascular disease risk.

TABLE 65.18

Vitamin C Intake Associated with Reduced Cardiovascular Disease Risk (Prospective Cohort Studies)

Reference	Population (Duration)	Endpoint (Events)	Risk and Associated Dietary Intake of Vitamin C
Enstrom[143]	3119 Men and women (10 y)	CVD (127 deaths)	>250 compared with < 250 mg/d: no ↓ risk
Enstrom[144] and Enstrom[145]	4479 Men (10 y) 6809 Women (10 y)	CVD (558 deaths) CVD (371 deaths)	>50 mg/d + vitamin supplement: ↓ risk by 42% >50 mg/d + vitamin supplement: ↓ risk by 25%
Manson[146] and Manson[147]	87,245 Female nurses (8 y)	CAD (552 cases) Stroke (183 cases)	>359 compared with <93 mg/d: ↓ risk by 20% (NS) >359 compared with <93 mg/d: ↓ risk by 24%
Rimm[148]	39,910 Male health professionals (4 y)	CAD (667 cases)	392 compared with 92 mg/d median: no ↓ risk
Fehily[149]	2512 Men (5 y)	CVD (148 cases)	>67 compared with < 35 mg/d: ↓ risk 37% (NS)
Knekt[150]	2748 Finnish men (14 y) 2385 Finnish women (14 y)	CAD (186 deaths) CAD (58 deaths)	>85 compared with < 60 mg/d: no ↓ risk >91 compared with < 61 mg/d: ↓ risk by 51%
Gale[151]	730 UK elderly men and women (20 y)	Stroke (125 deaths) CAD (182 deaths)	>45 compared with < 28 mg/d: ↓ risk by 50% >45 compared with < 28 mg/d: ↓ risk by 20% (NS)
Kritchevsky[152]	4989 Men (3 y) 6318 Women (3 y)	Carotid atherosclerosis Carotid atherosclerosis	>982 compared with < 56 mg/d: ↓ intima thickness >728 compared with < 64 mg/d: ↓ intima thickness
Pandey[153]	1556 Men (24 y)	CAD (231 deaths)	>113 compared with < 82 mg/d: ↓ risk by 25%
Kushi[154]	34,486 Women (7 y)	CAD (242 deaths)	>391 compared with < 112 mg/d (total)2 : no ↓ risk, >196 compared with < 87 mg/d (dietary): no ↓ risk, regular supplement compared with no supplement: no ↓ risk
Losconczy[155]	11,178 Elderly men and women (6 y)	CAD (1101 deaths)	Regular supplement compared with no supplement: no ↓ risk
Sahyoun[156]	725 Elderly men and women (10 y)	CVD (101 deaths)	>388 compared with <90 mg/d: ↓ risk by 62% (NS)
Mark[157]	29,584 Chinese men (5 y)	Stroke	180 mg/d supplement: no ↓ risk (+ 30 μg Mo/d cosupplement)

Note: CVD = Cardiovascular disease; CAD = Coronary artery disease.

Adapted from Carr AC, Frei B. *Am J Clin Nutr* 69: 1086; 1999.

Table 65.19 (adapted from Carr[142]) lists important prospective studies of vitamin C intake associated with reduced cancer risk.

Several epidemiologic studies that have investigated the association of vitamin C intake with the incidence of cataract are discussed in Section 62.

Vitamin D

Vitamin D is an essential element in the maintenance of healthy bones because it helps optimize calcium absorption and prevents increased parathyroid hormone (PTH) secretion.[168] High PTH levels stimulate resorption of bone, which may result in a gradual weakening of bones (osteomalacia) leading to an increase in the incidence of fractures.

Increasing evidence suggests that vitamin D is deficient in a large portion of the elderly population.[169] Vitamin D deficiency in the elderly may be caused by low exposure to sunlight, a reduced ability of the skin to synthesize cholecalciferol, and decreased dietary intakes.[170] This deficiency leads to hyperparathyroidism, bone loss, and increased incidence of fractures.[171] Vitamin D is synthesized in the skin by the action of ultraviolet light.[1] Vitamin D deficiency was found to be common in the elderly due to lack of mobility, which prevents adequate sun exposure.[172] Various studies have also demonstrated that hypovitaminosis D appears prevalent in the winter months due to a reduction in the number of hours spent outside coupled with the use of more protective clothing.[168,171-176]

The effect of age on vitamin D synthesis in the skin may be due to an age-related decline in the dermal production of 7-dehydrocholesterol, the precursor of previtamin D_3.[177] MacLaughlin and Holick compared the amount of previtamin D_3 produced by the skin of young subjects (8 and 18 years old) to the amount produced by the skin of elderly subjects (77 to 82 years).[178] This study revealed that aging appears to produce a greater than twofold reduction in previtamin D_3 production in subjects over 77 years of age.

Vitamin D deficiency, which can cause osteomalacia, is also important in the pathogenesis of age-related osteoporosis.[170] In a study of 3270 elderly women (mean age 84), 800 IU of vitamin D was given in combination with 1.2 g of elemental calcium to 1634 women, and 1636 women received a placebo. The number of hip fractures was reduced by 43% in the group treated with the combination of vitamin D and calcium after 18 months.[173,179] Treatment of the elderly with vitamin D may be a cost-effective method of maintaining bone density and reducing the incidence of osteoporotic fractures.[180]

Vitamin D as 1,25 dihydroxycholecalciferol appears to be potentially useful for people with psoriasis.[181] Topical application has worked well in some,[182-185] but not all, studies.[186,187] Use of vitamin D in psoriatic patients may work by helping skin cells replicate normally.

High doses of calcium combined with vitamin D have also been useful in treating cases of migraine[188,189] at a dose of 400 IU of vitamin D combined with 800 mg of calcium per day.

From epidemiological data, Giovannucci[190] reported that high circulating levels of $1,25(OH)_2$ vitamin D, the biologically active form, may decrease the risk of developing prostate cancer, and that diets high in calcium, phosphorus, and sulfur-containing amino acids from animal protein tend to decrease $1,25(OH)_2$ vitamin D. This effect of vitamin D on prostate cancer may be mediated via vitamin D receptors found on prostate cancer cells, and may be genotype specific.[191]

Animal models suggest that low vitamin D and calcium intake, as commonly found in Western-style diets, may be associated with an increased risk of both colon[192] and breast cancer,[193] although a long-term study of serum vitamin D levels and the incidence of breast

TABLE 65.19

Vitamin C Intake Associated with Reduced Cancer Risk (Prospective Cohort Studies)

Reference	Population (Duration)	Cancer Site (Events)	Risk and Associated Dietary Intake of Vitamin C
Shekelle[158]	1954 Men (19 y)	Lung (33 cases)	101 mg/d in noncases compared with 92 mg/d in cases (NS)
Enstrom[143]	3119 Men and women (10 y)	All cancers (68 deaths)	>250 compared with <250 mg/d no ↓ risk
Kromhout[159]	870 Dutch men (25 y)	Lung (63 deaths)	83–103 compared with <63 mg/d: ↓ risk by 64%
Knekt[160]	4538 Finnish men (20 y)	Lung (117 cases)	83 mg/d in noncases compared with 81 mg/d in cases (NS)
Enstrom[144]	4479 Men (10 y) 6869 Women (10 y)	All cancers (228 deaths) All cancers (169 deaths)	>50 mg/d + regular supplement: ↓ risk by 21% >50 mg/d + regular supplement: no ↓ risk
Shibata[161]	4277 Men (7 y) 7300 Women (7 y)	All cancers (645 cases) All cancers (690 cases)	>210 compared with <145 mg/d: no ↓ risk, 500 mg/d supplement compared with no supplement: no ↓ risk >225 compared with <155 mg/d: ↓ risk by 24%, 500 mg/d supplement compared with no supplement: no ↓ risk
Graham[162]	18,586 Women (7 y)	Breast (344 cases)	>79 compared with <34 mg/d: no ↓ risk
Hunter[163]	89,494 US female nurses (8 y)	Breast (1439 cases)	59 compared with <93 mg/d (total): no ↓ risk, regular supplement compared with no supplement: no ↓ risk, supplement >10 y compared with no supplement: no ↓ risk
Bostick[164]	35,215 Women (5 y)	Colon (212 cases)	>392 compared with <112 mg/d (total) : ↓ risk (NS), >201 compared with <91 mg/d (diet): no ↓ risk, >60 mg/d supplement compared with no supplement: ↓risk by 33%
Blot[165]	29,584 Chinese men and women (5 y)	Esophageal-stomach	120 mg/d supplement: no ↓ risk (+ 30 μg Mo/d cosupplement)
Pandey[153]	1556 Men (24 y)	All cancers (155 deaths)	>113 compared with <82 mg/d: ↓ risk by 39%
Losconczy[155]	11,178 Elderly men and women (6 y)	All cancers (761 deaths)	Regular supplement compared with no supplement: no ↓ risk
Sahyoun[156]	<725 Elderly men and women (10 y)	All cancers (57 deaths)	>388 compared with <90 mg/d: no ↓ risk
Kushi[166]	34,387 Women (5 y)	Breast (879 cases)	>392 compared with <112 mg/d (total): no ↓ risk, >198 compared with <87 mg/d (diet): no ↓ risk, regular supplement compared with no supplement: no ↓ risk
Yong[167]	3968 Men and women (19 y)	6100 Lung (248)	82 mg/d in noncases compared with 64 mg/d in cases

Adapted from Carr AC, Frei B. *Am J Clin Nutr* 69: 1086; 1999.

TABLE 65.20

Vitamin D — Established Benefits

Necessary for the proper formation of bones and teeth
Important for calcium absorption
Aids in the deposition of calcium and phosphorus into bones

TABLE 65.21

Vitamin D — Emerging Benefits

Use	Findings	Reference
Osteoporosis	Reduces the incidence of osteoporosis-related fracture	168-180
Psoriasis	Useful in topical application	181-187
Migraine	May be useful	188, 189
Cancer	May reduce the risk of prostate cancer	190-194
	Low intake is associated with an increased risk of colon and breast cancer	

cancer in humans did not reveal a direct association.[194] See Tables 65.20 and 65.21 for the established and emerging benefits of vitamin D.

Vitamin E

The emerging health benefits for vitamin E are extensive, and include reduction in cardiovascular risk, protection against certain forms of cancer, enhanced immunity, and a potential role in the treatment of certain neurological diseases. See Table 65.22 for the established benefits of vitamin E.

Early research identified that antioxidant scavengers such as vitamin E may reduce oxidative stress that can affect lipid metabolism, thereby producing oxidized low density lipoprotein (LDL) which is more atherogenic than the unoxidized form.[195,196] Because of this action, vitamin E was investigated to determine its efficacy in reducing the risk of cardiovascular disease.

Epidemiological studies found a significant inverse correlation between LDL levels, vitamin E concentration, and degree of coronary artery stenosis,[197] or mortality from ischemic heart disease.[198] The Cholesterol Lowering Atherosclerosis Study demonstrated that supplementary vitamin E intake greater than 100 IU per day was associated with a significant reduction in the progression of atherosclerosis in subjects not treated with lipid-lowering drugs.[199]

Two major epidemiological studies offer the most compelling evidence that vitamin E can reduce the incidence and mortality from coronary heart disease. Data from Stampfer et al.[200] and Rimm et al.[201] lend support to the growing body of evidence which suggests that antioxidants, especially fat-soluble antioxidants such as vitamin E, may protect against

TABLE 65.22

Vitamin E — Established Benefits

Essential for the formation of red blood cells, muscle, and other tissues
Necessary for the proper function of the nervous system
Protects the fat in tissues from oxidation

TABLE 65.23

Vitamin E and Coronary Heart Disease — Epidemiological Trials

Stampfer et al.[200]	87,000 Female nurses aged between 34-59 years	8 year follow-up	Vitamin E supplements for short periods had little apparent benefit, but those who took them for more than 2 years had a 41% reduction in the risk of major coronary artery disease
Rimm et al.[201]	40,000 US male health professionals aged between 40-75 years	4 year follow-up	Men consuming > 60 IU per day of vitamin E had a 36% decreased risk of CHD Men consuming > 100 IU per day for at least two years had a 37% reduced risk of CHD
HOPES Study[203]	2545 Women and 6996 men 55 years of age or older at risk for cardiovascular events	4.5 years	Vitamin E 400IU daily had no apparent effect on cardiovascular outcomes in patients at high risk for cardiovascular disease
GISSI-Prevenzione Study[204]	11,324 Men and women who survived recent myocardial infarction	3.5 years	Treatment with n-3 polyunsaturated fatty acids (PUFA) but not vitamin E 300 mg daily significantly lowered the risk of a fatal cardiovascular event

atherosclerosis by reducing the generation of oxidized LDL. Details of the two studies are listed in Table 65.23.

These data provide evidence of an association between a high intake of vitamin E and a lower risk of coronary heart disease in men. This was further corroborated by the Cambridge Heart Antioxidant Study (CHAOS)[202] wherein the investigators concluded that in patients with angiographically proven symptomatic coronary atherosclerosis, treatment with vitamin E substantially reduces the rate of non-fatal myocardial infarction, with beneficial effects apparent after one year of treatment. Recently, the results from two additional studies appear to contradict the benefit of vitamin E in cardiovascular disease.[203,204] These are also included in Table 65.23.

Although the effect of vitamin E in reducing cardiovascular mortality requires further corroboration, a number of other studies,[205-207] which investigated vitamin E along with other antioxidant vitamins, suggest that antioxidant vitamins reduce the risk of cardiovascular disease, with the clearest effect shown for vitamin E. In a related study, patients randomized after successful percutaneous transluminal coronary angioplasty to receive vitamin E 1200 IU per day for four months were found to have a 35.5% restenosis rate versus a 47.5% restenosis rate in patients receiving a placebo.[208]

Data from a number of epidemiologic studies have shown that individuals with higher intakes of vitamin E have lower risk of cancer. These data are summarized in Table 65.24.

Vitamin E is the major lipid-soluble antioxidant in humans, and its key function is to inhibit lipid peroxidation. Vitamin E deficiency is associated with decreased deep tendon reflexes, decreased proprioception, degeneration of neuronal axons, muscle weakness, and ataxia. Additionally, there is preferential central nervous system transport of vitamin E. These data suggest that vitamin E has a key role as a neurological antioxidant.

It has been hypothesized that Parkinson's patients may lack sufficient antioxidant protection and are susceptible to increased attack by free radicals.[228] A small, open trial of patients with early symptoms of Parkinson's disease was conducted in 1989 in which

TABLE 65.24

Vitamin E Levels and Cancer Incidence

Reference	Cancer Site	Sample Size	Location of Study	Correlation
Stahelin (1984)[207]	Lung, stomach, colon	4224	Switzerland	Vitamin E levels low in colon and stomach cancer cases
Wald (1984)[208]	Breast	5004	U.K.	Five time greater cancer risk for women with lowest vitamin E level
Salonen (1985)[209]	All sites	12,000	Finland	Risk 11.4 times higher with low vitamin E and selenium levels
Menkes (1986)[210]	Lung	25,802	U.S.	Risk 2.5 times higher with low vitamin E levels
Kok (1987)[211]	Lung, other sites	10,532	Holland	Risk 4.4 times higher for those with low vitamin E levels
Miyamoto (1987)[212]	Lung	55 Cancer cases	Japan	Higher cancer risk with low vitamin E levels
Wald (1987)[213]	All sites	22,000	U.K.	Vitamin E levels lower only in newly diagnosed cancer patients
Knekt (1988)[214]	All sites	21,172	Finland	Lower cancer risk with higher vitamin E levels
Knekt (1988)[215]	Gastrointestinal	36,265	Finland	Higher cancer risk with lower vitamin E levels
Knekt (1988)[216]	Reproductive organs	15,093	Finland	Cancer risk 1.6 times greater with lower vitamin E levels
Verreault (1989)[217]	Cervix	189 Cancer cases	U.S.	Lower risk of cervical cancer associated with higher vitamin E intake
LeGardeur (1990)[218]	Lung	59 Cancer cases	U.S.	Lung cancer patients have lower serum vitamin E levels
Buiatti (1990)[219]	Stomach	1016 Cancer cases	Italy	Risk 5 times higher with high vitamin E and C intake vs. low
Gridley (1990)[220]	Oropharynx	190 Cancer cases	U.S.	Lower risk associated with increased intake of vitamin E in men
Palan (1991)[221]	Cervix	116 Cancer cases	U.S.	Serum vitamin E levels lower in cervical cancer cases
Comstock (1991)[222]	Nine sites	25,802	U.S.	Vitamin E protective against lung cancer
Harris (1991)[223]	Lung, skin	96 Cancer cases	U.K.	Vitamin E levels lower in cancer patients
Knekt (1991)[224]	Lung	117 Cancer cases	Finland	Risk in nonsmokers associated with lower vitamin C and E intakes
Gridley (1992)[225]	Oropharynx	1103 Cancer cases	U.S.	Use of vitamin E supplements associated with reduced risk

individuals were given 400 to 3200 IU of vitamin E per day for up to seven years. Treated individuals were found to have an increased ability to carry out activities of daily living as compared to age-matched, unsupplemented controls.[229] A larger trial involved 160 patients with early symptoms of Parkinson's disease given 3200 IU of vitamin E and 3000 mg of vitamin C per day for an extended time. Using these two antioxidants prolonged the time to when treatment with levodopa was needed.[230]

The Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism (DATATOP) study[231,232] was a double-blind, placebo-controlled, multicenter trial involving 800 patients with early Parkinson's disease given deprenyl, (a monoamine oxidase inhibitor), and/or 2000 IU of vitamin E per day. The study showed that deprenyl alone increased the ability to perform activities of daily living after nine months of treatment; however, there was no effect seen from vitamin E alone or in combination with the deprenyl. An analysis of the results of this trial revealed that the type of vitamin E used was synthetic as opposed to natural vitamin E, which is much more lipid-soluble. This difference in vitamin E may have explained why more positive results were not seen in the antioxidant supplementation group.

The Rotterdam study was a nutritional epidemiological study of 5342 free-living individuals between the ages of 55 and 95, including 31 individuals with pre-existing Parkinson's disease. In examining dietary intakes, there was a significant correlation between the level of daily dietary intake of vitamin E, beta-carotene, and vitamin C and protection against development of Parkinson's disease.[233]

Large intakes of vitamin E are associated with slowing the progression of Alzheimer's disease, according to research from the Alzheimer's Disease Cooperative Study. A two-year study of 341 individuals with Alzheimer's disease of moderate severity found that 2000 IU per day of vitamin E extended the time patients were able to care for themselves compared to that of those taking a placebo.[234]

Vitamin K

Vitamin K is the collective name for a group of compounds all of which contain the 2-methyl-1,4-naphthoquinone moiety. Human tissue contains phylloquinone (vitamin K_1), several menaquinones (types of vitamin K_2), as well as menadione (vitamin K_3).[235] Phytonadione is the name given to common pharmaceutical preparations.[236]

Compounds with vitamin K activity are essential for the formation of prothrombin and at least five other proteins involved in the regulation of blood clotting including Factors VII, IX, and X, as well as protein C and protein S. Although vitamin K is also required for the biosynthesis of several other proteins found in the plasma, bone, and kidney, defective coagulation of the blood is the only major known sign observed in vitamin K deficiency states.[235,237] Vitamin K deficiency in adults is frequently associated with fat malabsorption syndromes.

Although a wide variation exists, decreased vitamin K levels are generally associated with a decrease in the proportion and absolute amount of carboxylated osteocalcin. Osteocalcin is a vitamin K-dependent protein found in bone matrix, and its levels are a reflection of osteoblastic activity. It has therefore been hypothesized that decreased vitamin K levels might be related to an increased risk for osteoporosis.[238,239,240]

Vitamin K deficiency has been shown to be associated with decreased bone mass in post-menopausal women with aortic atherosclerosis, but not in a similar group without

TABLE 65.25

Vitamin K — Established Benefits

Necessary for normal blood clotting
Calcium metabolism

TABLE 65.26

Vitamin K — Emerging Benefits

Use	Findings	Reference
Osteocalcin formation	Decreased levels are associated with decreased osteocalcin	236-239
Osteoporosis	Possible effect in improving bone mass	240, 241

atherosclerosis. This may be due to the fact that gamma-carboxyglutamate, an amino acid formed by vitamin K action, is known to be involved with regulation of calcification in both bone tissue and atherosclerotic vessel walls, and that abdominal calcification is known to be associated with decreased vitamin K status.[241] Patients treated with warfarin appear to have structural alterations in circulating osteocalcin, which suggests the pathophysiological implication of an association of the use of warfarin with osteoporosis.[242]

Low vitamin K intake is known to be associated with an increased risk of hip fracture in women.[242] Vitamin K supplementation in a group of 20 postmenopausal women with osteoporotic fractures resulted in improved carboxylation of osteocalcin.[243] In summary, these studies suggest a possible link between vitamin K deficiency and osteoporosis. Administration of vitamin K appears to improve a key biochemical parameter that has been associated with decreased bone mass; namely, carboxylated osteocalcin. It is unclear whether the administration of vitamin K has beneficial effects in improving bone mass or preventing osteoporosis or osteoporosis-related fractures. See Tables 65.25 and 65.26 for established and emerging benefits of vitamin K.

Calcium

There is an abundance of evidence that adequate dietary calcium intake minimizes bone loss in postmenopausal women[244-248] and reduces the increased risk of fracture associated with osteoporosis.[249-252] Additionally, calcium supplementation has been demonstrated to augment the bone-preserving effect of estrogen replacement therapy in postmenopausal women.[253,254] The U.S. Food and Drug Administration permits a claim for calcium in the prevention and treatment of osteoporosis.

Use of vitamin D in combination with calcium supplementation is particularly important in preventing loss of bone in women who are borderline deficient[255] and reducing the incidence of fractures in the advanced elderly.[256,257,258] Vitamin D is an essential element in the maintenance of healthy bones because it helps optimize calcium absorption and prevents increased parathyroid (PTH) secretion.[259] High PTH levels stimulate resorption of bone that may result in a gradual weakening of bones leading to an increase in the incidence of fractures.

Calcium supplementation has recently been shown to help prevent colorectal adenomas,[260,261] which are precursors of colon cancer (see also Mobarhan[262] and Lipkin et al.[263] for an excellent review of this subject, and a separate review by Lipkin and Newmark[264]

TABLE 65.27

Calcium — Established Benefits

Regulates heart beat
Involved in muscle contraction and nerve transmissions
Assists in blood clotting
Required for bone formation

TABLE 65.28

Calcium — Emerging Benefits

Use	Findings	Reference
Osteoporosis and osteoporotic fracture	Increased bone mass, decreased risk of fracture	242-257
Colon cancer, breast cancer	Reduces the incidence of colorectal adenomas	258-262
Premenstrual syndrome	Reduces severity of PMS symptoms	263
Improved hormone replacement therapy	Permits lower dose of HRT to be used	264
Hypertension	May lower high blood pressure in individuals with calcium-poor diet	265, 266

on vitamin D, calcium, and breast cancer) and to effectively reduce premenstrual symptoms associated with the luteal phase.[265] The administration of 1000 mg of calcium in the presence of normal blood levels of vitamin D has also been demonstrated to permit a lower dose of hormone replacement therapy (HRT) to increase bone density and provide a bone-sparing effect in elderly women similar to or better than that provided by higher-dose HRT without calcium and vitamin D supplementation.[266]

The value of calcium in control of blood pressure is debatable. Despite conflicting data, meta-analysis of a large number of observational and randomized controlled clinical trials indicates that calcium intake has an impact in reducing blood pressure, particularly in persons regularly consuming low levels of dietary calcium.[267,268] Additional work in this area remains to be done. See Tables 65.27 and 65.28 for established and emerging benefits of calcium.

Magnesium

Magnesium appears to be directly involved in bone metabolism, helping in the formation of bone and indirectly interfacing with hormones regulating bone metabolism. Tranquilli et al. demonstrated that both daily intake and bone mineral content of calcium, phosphorus, and magnesium were significantly reduced in a group of postmenopausal women with osteoporosis compared to non-osteoporotic controls.[269] Additionally, supplementation with magnesium has been shown to help increase bone density in postmenopausal osteoporosis.[270]

Magnesium supplements — typically 350 to 500 mg per day — lower blood pressure,[272] but these findings are inconsistent.[273,274] Results appear to be particularly effective in people who are taking diuretics.[275]

Women with PMS are often deficient in magnesium.[276,277] Supplementation with magnesium may help reduce symptoms.[278,279]

Magnesium can increase blood supply by acting as a vasodilator. At least one trial has found that magnesium supplementation of 250 mg per day increases walking distance for

TABLE 65.29

Magnesium — Established Benefits

Regulates heart beat, muscle contractions, and nerve transmissions
Aids in calcium absorption and the deposition of calcium and phosphorus into bones

TABLE 65.30

Magnesium — Emerging Benefits

Use	Findings	Reference
Osteoporosis	Helps increase bone mass	267, 268
Hypertension	May help lower blood pressure, especially where magnesium has been depleted	269-273
PMS symptoms	Deficiency is associated with PMS symptoms	274-277
Intermittent claudication	May respond to magnesium	278

people with intermittent claudication.[280] See Tables 65.29 and 65.30 for established and emerging benefits of magnesium.

Zinc

Zinc supplementation may be helpful in promoting wound healing in individuals who are zinc deficient. A dose of 220 mg of zinc sulfate (equivalent to 50 mg of elemental zinc) given three times a day for seven to eight weeks has been shown to improve wound healing in zinc-deficient patients.[281,282] There is no evidence that zinc supplementation benefits wound healing in individuals whose zinc nutriture is adequate.

Although popular in some countries, the role of zinc supplementation in improving male sexual function is unproven. Studies have shown that zinc is involved in the reproductive process for humans as well as animals. In humans, zinc is thought to be necessary for the formation and maturation of sperm, for ovulation, and for fertilization. High levels of zinc are found in most male reproductive organs, with the highest concentrations located in the prostate. In animal studies, the normal male testis and prostate contain a high concentration of zinc, and zinc deficiency has been shown to lead to defects in sperm along with a depletion of testosterone.[283-286] For men with low testosterone levels, zinc supplementation raises testosterone and increases fertility.[287] For men with low semen zinc levels, zinc supplements may increase both sperm counts and fertility.[288] Most published studies involve infertile men who have taken zinc supplements for at least several months.

Zinc deficiency in humans has been shown to cause retarded growth and slowed skeletal development.[289] Yamaguchi demonstrated that reduced bone growth is sometimes found in conditions associated with zinc deficiency. Additionally, he demonstrated that zinc has a stimulatory effect on bone growth.[290] Other studies have demonstrated a significant correlation between zinc content and bone strength.[291,292] Zinc has an important role in osteogenesis and bone metabolism, although the exact mechanism remains unknown.[289]

Studies have examined the role of zinc in the treatment of anorexia nervosa and in lozenge form to help decrease the duration of symptoms of the common cold. More research is needed to fully characterize the possible benefits of zinc in these conditions. Recent data from cohort epidemiological studies show zinc to be weakly protective against

TABLE 65.31

Zinc — Established Benefits

Involved in protein metabolism
Necessary for insulin synthesis
Important for night vision

TABLE 65.32

Zinc — Emerging Benefits

Use	Findings	Reference
Aids in wound repair	Useful in cases of deficiency	279, 280
Male infertility	No proven benefit	281-286
Osteoporosis	May help increase bone strength	287-290
Age-related macular degeneration	Possibly protective	291-292
Immunity	Increases immune response	293-297

the development of some forms of early age-related macular degeneration (AMD),[293] although this effect is not proven.[294] (See Section 62.)

Zinc also helps support immune function. An older comprehensive review of the literature by Good et al.[295] as well as information from Chandra and McBean[296] and Prasad et al.[297] suggest that inadequate diet, defective absorption of zinc, disturbances in zinc metabolism, or abnormally increased losses of zinc may be associated with deficits in immune function. Low-dose supplementation of zinc (20 mg) and selenium (100 μg) has been shown to provide significant improvement in elderly patients by increasing humoral response after vaccination.[298] Improved cell-mediated immune response was seen following the administration of zinc 25 mg in an institutionalized elderly population.[299] In this study, a similar effect was not seen for vitamin A 800 μg. See Tables 65.31 and 65.32 for established and emerging benefits of zinc.

Selenium

An epidemiological association between increased selenium intakes and reduced cancer risk, as well as the antioxidant role of selenium in glutathione peroxidase, have provided a basis for research on the potential anticarcinogenic effects of selenium. While the exact mechanism by which selenium exerts its preventative effect against certain types of cancer in humans is unknown, selenium supplementation in animal experiments has been shown to result in enhanced primary immune response in mice, as measured by the plaque-forming cell test and hemagglutination.[300] The addition of supplemental amounts of selenium to the diet has been demonstrated to increase humoral antibody production in swine in response to an antigenic challenge with sheep red blood cells.[301] Selenium deficiency is also known to cause impaired mitogen response in cultures of murine spleen cells.[302]

Two clinical intervention trials published to date have demonstrated that selenium, in combination with other nutrients, may reduce cancer risk. In one study,[303] daily administration of 50 μg of selenium in combination with vitamin E and beta-carotene resulted in a moderate reduction in the risk of total mortality, total cancer mortality and stomach cancer mortality. More recently, Clark et al.[304] showed that treatment with 200 μg of

TABLE 65.33

Selenium — Established and Emerging Benefits

Established
Needed for proper immune system response
Helps prevent Keshan disease (a cardiomyopathy)
Antioxidant via glutathione peroxidase
Emerging
Prevents certain types of cancer

selenium per day significantly decreased total mortality and mortality from lung cancer, as well as the incidence of colorectal and prostate cancer.

To test whether supplemental dietary selenium is associated with changes in the incidence of prostate cancer, in another study by Clark, a total of 1312 men with a history of either basal cell or squamous cell carcinoma were randomized to a daily supplement of 200 μg of selenium or a placebo.[305] Patients were treated for a mean of 4.5 years and followed for a mean of 6.4 years. There was no significant change in incidence for the primary endpoints of basal and squamous cell carcinoma of the skin; however, selenium treatment was associated with a significant reduction (63%) in the secondary endpoint of prostate cancer incidence. There were also significant health benefits for other secondary endpoints of total cancer mortality and the incidence of total, lung, and colorectal cancer.

In another study,[306] patients with histories of basal/squamous cell carcinomas of the skin were assigned randomly to either daily oral supplements of selenium-enriched yeast (200 μg Se/day) or a placebo. The results of this study indicate that supplemental selenium intake did not significantly affect the incidence of recurrent basal/squamous cell carcinomas of the skin; however, selenium treatment was associated with reductions in total mortality, mortality from all cancers combined, and the incidence of all cancers combined, lung cancer, colorectal cancer, and prostate cancer.

The consistency of these findings over time strongly suggests that there is an anticancer benefit to selenium supplementation, particularly in reducing the incidence of prostate cancer. An excellent review of selenium and prostate cancer prevention[307] and a review of the mechanisms of the chemopreventive effects of selenium[308,309] have been published. See Table 65.33 for the established and emerging benefits of selenium.

Chromium

Chromium is an essential trace element that is a constituent of glucose tolerance factor and is required for effective insulin action in humans. Data in the literature are equivocal, suggesting a positive benefit of chromium supplementation on glycemic control in diabetes, but a consistent beneficial effect of chromium supplementation remains unproven.

The American Diabetes Association (ADA) does not currently recommend supplementation with chromium for individuals with diabetes. The ADA position statement, "Nutrition Recommendations and Principles for People with Diabetes Mellitus,"[310] states:

> The only known circumstance in which chromium replacement has any beneficial effect on glycemic control is for people who are chromium deficient as a result of long-term chromium-deficient parenteral nutrition. However, it appears that most people with diabetes are not chromium deficient and, therefore, chromium supplementation has no known benefit.

TABLE 65.34

Chromium — Established and Emerging Benefits

Established
Necessary for DNA synthesis
Important for cell formation
Prevents certain types of anemias
Helps maintain the function of the intestinal tract
Emerging
Hyperglycemic control
Increased bone mass
Control of hypertension
Improved lipid profiles

Further studies to assess the effects of dietary chromium supplementation on insulin sensitivity, as well as on other processes such as increased bone mass, improved blood pressure, and lipid profiles in humans are needed.

For further information on this topic the reader is referred to an excellent review by Schmidt Finney[311] as well as an extensive bibliography of material on this subject.[312-329] See Table 65.34 for the established and emerging benefits of chromium.

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