TREATMENT VITAMIN A DEFICIENCY

Any stage of xerophthalmia should be treated with 60 mg (or RAE) of vitamin A in oily solution, usually contained in a soft-gel capsule. The same dose is repeated 1 and 14 days later. Doses should be reduced by half for patients 6–11 months of age. Mothers with night blindness or Bitot's spots should be given vitamin A orally–either 3 mg daily or 7.5 mg twice a week for 3 months. These regimens are efficacious, and they are less expensive and more widely available than injectable water-miscible vitamin A. A common approach to prevention is to provide vitamin A supplementation every 4–6 months to young children and infants (both HIV-positive and HIV-negative) in high-risk areas. Infants 6–11 months of age should receive 30 mg vitamin A; children 12–59 months of age, 60 mg. For reasons that are not clear, vitamin A supplementation has not proven useful in high-risk settings for preventing morbidity or death among infants 1–5 months of age.

Uncomplicated vitamin A deficiency is rare in industrialized countries. One high-risk group—extremely low-birth-weight (<1000-g) infants—is likely to be vitamin A–deficient and should receive a supplement of 1500 μg (or RAE) three times a week for 4 weeks. Severe measles in any society can lead to secondary vitamin A deficiency. Children hospitalized with measles should receive two 60-mg doses of vitamin A on two consecutive days. Vitamin A deficiency most often occurs in patients with malabsorptive diseases (e.g., celiac sprue, short-bowel syndrome) who have abnormal dark adaptation or symptoms of night blindness without other ocular changes. Typically, such patients are treated for 1 month with 15 mg/d of a water-miscible preparation of vitamin A. This treatment is followed by a lower maintenance dose, with the exact amount determined by monitoring serum retinol.

No specific signs or symptoms result from carotenoid deficiency. It was postulated that β-carotene would be an effective chemopreventive agent for cancer because numerous epidemiologic studies had shown that diets high in β-carotene were associated with lower incidences of cancers of the respiratory and digestive systems. However, intervention studies in smokers found that treatment with high doses of β-carotene actually resulted in more lung cancers than did treatment with placebo. Non–provitamin A carotenoids such as lutein and zeaxanthin have been suggested to confer protection against macular degeneration, and one large-scale intervention study did not show a beneficial effect except in those with a low lutein status. The use of the non–provitamin A carotenoid lycopene to protect against prostate cancer has been proposed. Again, however, the effectiveness of these agents has not been proved by intervention studies, and the mechanisms underlying these purported biologic actions are unknown.

Selective plant-breeding techniques that lead to a higher provitamin A content in staple foods may decrease vitamin A malnutrition in low-income countries. Moreover, a recently developed genetically modified food (Golden Rice) has an improved β-carotene–to–vitamin A conversion ratio of ~3:1.

Toxicity The acute toxicity of vitamin A was first noted in Arctic explorers who ate polar bear liver and has also been seen after administration of 150 mg to adults or 100 mg to children. Acute toxicity is manifested by increased intracranial pressure, vertigo, diplopia, bulging fontanels (in children), seizures, and exfoliative dermatitis; it may result in death. Among children being treated for vitamin A deficiency according to the protocols outlined above, transient bulging of fontanels occurs in 2% of infants, and transient nausea, vomiting, and headache occur in 5% of preschoolers. Chronic vitamin A intoxication is largely a concern in industrialized countries and has been seen in otherwise healthy adults who ingest 15 mg/d and children who ingest 6 mg/d over a period of several months. Manifestations include dry skin, cheilosis, glossitis, vomiting, alopecia, bone demineralization and pain, hypercalcemia, lymph node enlargement, hyperlipidemia, amenorrhea, and features of pseudotumor cerebri with increased intracranial pressure and papilledema. Liver fibrosis with portal hypertension and bone demineralization may result from chronic vitamin A intoxication. Provision of vitamin A in excess to pregnant women has resulted in spontaneous abortion and in congenital malformations, including craniofacial abnormalities and valvular heart disease. In pregnancy, the daily dose of vitamin A should not exceed 3 mg. Commercially available retinoid derivatives are also toxic, including 13-*cis*-retinoic acid, which has been associated with birth defects. Thus contraception should be continued for at least 1 year and possibly longer in women who have taken 13-*cis*-retinoic acid.

In malnourished children, vitamin A supplements (30–60 mg), in amounts calculated as a function of age and given in several rounds over 2 years, are considered to amplify nonspecific effects of vaccines. However, for unclear reasons, there may be a negative effect on mortality rates in incompletely vaccinated girls.

High doses of carotenoids do not result in toxic symptoms but should be avoided in smokers due to an increased risk of lung cancer. Very high doses of β-carotene (~200 mg/d) have been used to treat or prevent the skin rashes of erythropoietic protoporphyria. Carotenemia, which is characterized by a yellowing of the skin (in creases of the palms and soles) but not the sclerae, may follow ingestion of >30 mg of β-carotene daily. Hypothyroid patients are particularly susceptible to the development of carotenemia due to impaired breakdown of carotene to vitamin A. Reduction of carotenes in the diet results in the disappearance of skin yellowing and carotenemia over a period of 30–60 days.

VITAMIN D

The metabolism of the fat-soluble vitamin D is described in detail in Chap. 423. The biologic effects of this vitamin are mediated by vitamin D receptors, which are found in most tissues; binding with these receptors potentially expands vitamin D actions on nearly all cell systems and organs (e.g., immune cells, brain, breast, colon, and prostate) as well as exerting classic endocrine effects on calcium metabolism and bone health. Vitamin D is thought to be important for maintaining normal function of many nonskeletal tissues such as muscle (including heart muscle), for immune function, and for inflammation as well as for cell proliferation and differentiation. Studies have shown that vitamin D may be useful as adjunctive treatment for tuberculosis, psoriasis, and multiple sclerosis or for the prevention of certain cancers. Vitamin D insufficiency may increase the risk of type 1 diabetes mellitus, cardiovascular disease (insulin resistance, hypertension, or low-grade inflammation), or brain dysfunction (e.g., depression). However, the exact physiologic roles of vitamin D in these nonskeletal diseases and the importance of these roles have not been clarified.

The skin is a major source of vitamin D, which is synthesized upon skin exposure to ultraviolet B radiation (UV-B; wavelength, 290–320 nm). Except for fish, food (unless fortified) contains only limited amounts of vitamin D. Vitamin D_2 (ergocalciferol) is obtained from plant sources and is the chemical form found in some supplements.

Deficiency Vitamin D status has been assessed by measuring serum levels of 25-dihydroxyvitamin D ($25[OH]_2$ vitamin D); however, there is no consensus on a uniform assay or on optimal serum levels. The optimal level might, in fact, differ according to the targeted disease entity. Epidemiologic and experimental data indicate that a $25(OH)_2$ vitamin D level of >20 ng/mL (≥50 nmol/L; to convert ng/mL to nmol/L, multiply by 2.496) is sufficient for good bone health. Some experts advocate higher serum levels (e.g., >30 ng/mL) for other desirable endpoints of vitamin D action. There is insufficient evidence to recommend combined vitamin D and calcium supplementation as a primary preventive strategy for reduction of the incidence of fractures in healthy men and premenopausal women.

Risk factors for vitamin D deficiency are old age, lack of sun exposure, dark skin (especially among residents of northern latitudes), fat malabsorption, and obesity. *Rickets* represents the classic disease of vitamin D deficiency. Signs of deficiency are muscle soreness, weakness, and bone pain. Some of these effects are independent of calcium intake.