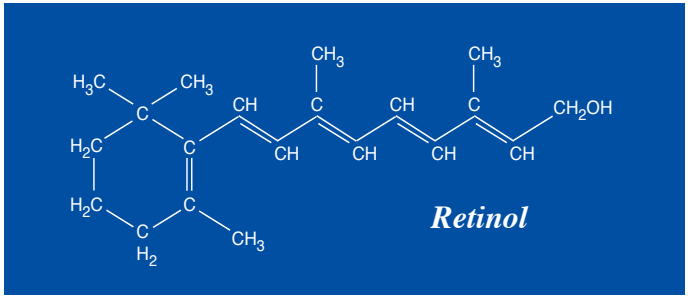

Vitamin A

Introduction

Vitamin A is both a fat-soluble vitamin and a hormone, contributing to the visual pigment rhodopsin and controlling gene transcription that allows for the normal proliferation and differentiation of epithelial cells. Vitamin A also modulates the immune response through lymphopoesis, apoptosis, cytokine production, the function of neutrophils, and lymphocytes, and immunoglobin production.[1] Therapeutically, retinoids, the active metabolites of retinoic acid (naturally occurring vitamin A) are effective chemopreventive agents in the treatment of skin, head and neck, breast, and liver cancers and certain forms of leukemia.

Biochemistry and Mechanisms of Action

Vitamin A exists in animal products as retinyl esters and in plant foods as the precursor carotenoid family. Beta-carotene is cleaved to retinyl esters and retinoic acid in the enterocyte of the small intestine and packaged into chylomicrons along with retinol from preformed vitamin A for transport to the liver for storage as retinol in hepatic stellate cells.[2] When needed, retinol is transported to tissues bound to retinol binding protein (a zinc-dependent protein). Zinc deficiency disturbs normal retinol metabolism, and supplementation with zinc has been shown to treat retinol-resistant night-blindness.[3] In the eye, retinol is oxidized to retinaldehyde, the basis of the visual pigments rhodopsin and iodopson. It is also oxidized to retinoic acid, the parent compound of natural retinoids.[4] Two specific isomers, all-trans-retinoic acid and 9-cis-retinoic acid, have been found to bind to specific receptors in the nucleus of target cells and assist in regulating the cell replication cycle through transcription factors-tumor suppressor proteins p53 and p105, which are both strong inhibitors of uncontrolled cell growth.[5]

Retinoids, through their interaction with nuclear retinoic acid receptors in tissue, control gene expression and promote normal proliferation and differentiation of epithelial tissue, particularly mucous membrane epithelium.

Vitamin A functions in the immune system in the modulation of diverse pathways: in the expression of mucins and keratins, lymphopoesis, cytokine production, neutrophil maturation and function, the functional expression of natural killer cells, monocytes and macrophages, T and B lymphocytes, and immunoglobin production.[6]

Deficiency States and Symptoms

Vitamin A deficiency is internationally profound and widespread, and responsible for one

third of all mortality in infants and preschool-age children worldwide.[6] Although morbidity and mortality are usually referred to as a problem only in developing countries, it has also been documented in children and adults in the United States. In low income young women aged 19-34, over half consume less than 70 percent of the RDA for vitamin A and one-third consume less than 50 percent of the RDA.[7]

Low serum retinol levels are found in Crohn's disease patients,[8] in alcoholics,[9] diabetics,[10] and in juvenile arthritics.[11] Lowered vitamin A levels may also occur with overuse of laxatives, chronic intake of mineral oil, chronic cortisone usage, cigarette smoking, zinc deficiency, vitamin D deficiency, excessive iron consumption, organophosphate (DDT and PCB) exposure, cold exposure, nitrate ingestion, and excessive consumption of refined carbohydrates.[12] Vitamin A deficiency is related to increased susceptibility to measles, malaria, tuberculosis, and other respiratory and intestinal infectious diseases.[6]

Clinical Applications

Diseases of the Eye

Vitamin A deficiency has been linked to ocular disorders that result from oxidative damage to the photoreceptor cells and the pigmented epithelium of the retina. Night blindness, age-related macular degeneration, retinitis pigmentosa, retinopathy, and xeropthalmia are related to either vitamin A deficiency or impaired vitamin A metabolism.[13-15] Retinitis pigmentosa occurs as a result of altered vitamin A metabolism without lowered blood retinol levels; however, Vitamin A supplementation can be helpful in individuals with this condition. A long-term study utilizing 15,000 IU supplemental vitamin A daily slowed the rate of decline of retinal function in these patients.[15]

Cervical Dysplasia

Vitamin A regulates genes that control squamous proliferation. Vitamin A deficiency in animal models caused squamous metaplasia of columnar cervical cells.[16] Low levels of vitamin A are also very common in smokers with cervical dysplasia.[17] When compared to controls, women with cervical dysplasia have been found to have significantly lower levels of serum retinol and serum beta-carotene.[18,19] Women infected with HIV have a higher prevalence of vitamin A deficiency than the general population. In a study of 1,314 HIV-positive women, this deficiency was significantly associated with cancerous cervical squamous intraepithelial lesions (SILs).[20] The association remained independent of markers of HIV disease stage, status of human papilloma virus infection, and overall nutritional status. Vitamin A deficiency status was also independent of CD4 count or viral load. Cervical SILs were almost twice as likely in women with abnormally low vitamin A levels (15 percent of the study population).

Retinoic acid was used topically and intravenously to reverse mild-to-severe cervical dysplasia in 96.29 percent of a study population.[21] Topical treatment with all-trans retinoic acid alone has been equally effective in moderate dysplasia.[22]

Cancer

Vitamin A has been used in the prevention and treatment of specific pre-malignant, malignant, and recurrent neoplasms.[23] Retinoic acid has been found to be effective in suppressing pre-malignant cells in oral leukoplakia, laryngeal dysplasia, bronchial metaplasia and dysplasia, and cervical dysplasia.[24] Retinoids prevent the development of second primary cancers in head and neck and lung cancer patients who have been treated for a primary tumor.[25] Retinoids, in combination with interferons, have been used to treat cutaneous squamous cell carcinoma, with a 50-68 percent response rate.[26] Retinoic acid therapy has also been shown to significantly improve the survival of children with neuroblastoma by suppressing residual disease after chemotherapy.[27]

A three-year clinical study using retinoic acid in patients with xeroderma pigmentosum resulted in a significant reduction in the number of new and recurrent skin tumors (basal cell and squamous cell carcinoma).[28] The tumor frequency increased 8.5-fold after retinoic acid was discontinued. Acute promyelocytic leukemia has been shown to respond to all-trans retinoic acid added to chemotherapy. Survival rates in two randomized studies of 1,000 patients treated with all-trans retinoic acid (45 mg/m^2 per day) in addition to chemotherapy showed complete remission rates of 93 and 94 percent.[29,30]

Because levels of retinoic acid used in oncology are very high, (average dose 45-50 mg/m^2 body surface area per day, up to 330,000 IU daily) trials have used synthetic retinoids in an attempt to moderate toxicity symptoms.[31]

Combination trials of vitamin A and interferon have been used in human studies on squamous cell cancer, cervical cancer, renal cell carcinoma, chronic myelogenous leukemia, and laryngeal dysplasia.[32] A recent study in patients with head and neck squamous cell tumors used alpha-tocopherol in an attempt to moderate toxicity of both alpha-interferon and 13-cis-retinoic acid.[33] Antioxidants, specifically vitamin E, have been theorized to limit vitamin A toxicity symptoms. In a trial that attempted to prevent recurrence of advanced head and neck tumors or second primary tumors, patients were given 167,000 IU/m^2 body surface area of 13-cis-retinol (approximately 300,000 IU per day) and 1,200 IU alpha-tocopherol, in addition to interferon-alpha daily for 12 months. Thirty-eight of 44 patients completed the 12 months of treatment with only mild-to-moderate side effects. Median 1-and 2-year disease-free survival rates were 91 percent and 84 percent, respectively.

Menorrhagia

In a South African study of 71 women with menorrhagia, low serum retinol levels were found in the majority of those studied.[34] Treatment of 40 patients with 25,000 IU vitamin A twice daily for 15 days completely alleviated symptoms in 58 percent and significantly reduced blood loss in 35 percent.

Infectious Diseases

Because vitamin A maintains the integrity of mucous membranes, increases surface glycoproteins, is integral to the production of secretory IgA, and is involved in humoral and cellular immunity, its application in infectious diseases logically follows.[6]

In a U.S. study, 50 percent of children diagnosed with acute measles virus were vitamin A deficient.[35] Therapeutic use of vitamin A in measles has been confirmed in multiple studies where it has reduced mortality by at least 50 percent.[36] Infection with respiratory syncytial virus has been correlated with low vitamin A levels in children whose blood levels of vitamin A were normalized with the administration of 25,000 IU.[37] Intramuscular injections of 2,000 IU daily for the first month of life in very-low-birth-weight pre-term infants have been used to effectively decrease risk for bronchopulmonary dysplasia.[38]

Children with no indication of vitamin A deficiency (normal serum retinol levels), but susceptibility to respiratory infections, were given 3,800 IU vitamin A three times weekly for 11 months, resulting in a 20-percent lower incidence of respiratory infections.[39]

HIV Infection

Vitamin A deficiency occurs commonly in HIV infection and worsens as the disease progresses.[40] Low levels are specifically problematic in pregnant women and are directly linked to infant mortality and vertical transmission. Vitamin A-deficient mothers are 3.7 times more likely to transmit the virus to their children.[41] Seventy percent of children born to HIV-positive mothers are vitamin A deficient.[42] The use of supplemental vitamin A prior to and at the time of birth has reduced the likelihood of transmission in pre-term infants by almost 50 percent.[43]

Drug-Nutrient Interactions

There is a risk of hypervitaminosis if vitamin A supplements are taken with retinoid drugs (used for skin disorders). Cholestyramine, colestipol hydrochloride, (both cholesterol lowering drugs) and mineral oil (as a laxative) may reduce absorption of vitamin A. People taking these drugs over a long period should consider taking a vitamin A supplement.[44]

Side Effects and Toxicity

Vitamin A is a teratogen; however supplementation of oil-soluble vitamin A in excess of 10,000 IU daily during pregnancy has been associated with a low incidence (less than 20 in the past 30 years) of documented birth defects.[45] The recommended dose for pregnant women in the U.S. is up to 8,000 IU daily, even though most studies have shown at least 20,000 IU daily is necessary to increase teratogenic risk.[46] One study in which women took daily oral doses of 30,000 IU did not significantly increase blood retinoic acid levels above physiologic normal ranges.[47] The main toxicity symptoms in chronic supplementation are headache, alopecia, chelosis, pruritis, hepatomegaly, bone and joint pain. After termination of intake, the majority of cases remit without permanent damage.[48] Toxicity symptoms after single pediatric doses of 165,000-330,000 IU of vitamin A are self-limited and non-life threatening (headaches, nausea, vomiting) and studies looking at toxicity of single doses of 100,000-200,000 IU in preschool children found minimal risk.[49]

The vast majority of chronic toxicity cases have occurred at levels of daily supplementation of 12,000 to 600,000 IU in children and 50,000 to1,000,000 IU in adults over a period of weeks to years. Vitamin A intolerance-toxicity symptoms occurring after chronic intakes at levels of 6,000 to 53,000 IU is less common and thought to be related to a genetic or metabolic defect in vitamin A handling.[50]

Dosage

Dosages in treatment of chronic pediatric respiratory infections range from 3,800 IU three times weekly in vitamin A nourished children to 200,000 IU single dose in suspected vitamin A deficiency.[39] In measles, with suspicion of vitamin A deficiency, the recommended protocol is 200,000 IU upon diagnosis and 200,000 IU two weeks later.[49] Recommended single doses in suspicion of vitamin A deficiency in pediatric chronic diarrhea or pediatric lower respiratory infection are 200,000 IU.

Adult RDA for vitamin A is 3,000 IU for men, 2,300 IU for women, and 2,500 IU for pregnant or reproductive age women. The Tolerable Upper Intake Levels (highest level of daily vitamin A intake that is likely to pose no risk of adverse health effects in almost all individuals) are 10,000 IU for men and women, and 9,300 IU for pregnant or reproductive age women.[51] Dosages for disease states are individualized and referenced in the clinical indications above.

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