VITAMIN A … FROM PHYSIOLOGY TO DISEASE PREVENTION

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ABSTRACT

Vitamin A is an essential micronutrient whose role in visual function has been known for thousands of years. The beneficial effects of vitamin A might have been recognized by the ancient Egyptians who treated eye disease with raw liver. They identified a connection between eye problems and the liver, which is the richest source of vitamin A. The well known basic function of vitamin A is the formation of retinal pigments of the eye. However, today, we know that vitamin A (retinol) and its biologically active derivatives, the retinoids, regulate key processes such as inhibition of cell proliferation, differentiation, apoptosis, shaping the embryo and organogenesis. On the other hand, either vitamin A deficiency or over-intake may be associated with serious health problems. Therefore use of vitamin A must be optimized to obtain the best prophylactic and treatment results. This review will shed the light of different important aspects regarding vitamin A in regulation of physiological body functions, pathological conditions resulting from decreased or chronic excessive administration and its use as an effective tool in prophylaxis and treatment of specific health problems.

INTRODUCTION

Vitamins are essential organic compounds required in very small amounts (micronutrients required in amounts of micrograms to milligrams) to maintain the fundamental functions of the body. The discovery of vitamin A stemmed from research dating back to 1906, indicating that factors other than carbohydrates, proteins, and fats were necessary to keep cattle healthy. In fact, vitamin A is a generic term for a large number of related compounds. Retinol (an alcohol) and retinal (an aldehyde) are often referred to as preformed vitamin A. Retinal can be converted by the body to retinoic acid, the form of vitamin A known to affect gene transcription. Retinol, retinal, retinoic acid, and related compounds are known as retinoids. Beta-carotene and other carotenoids that can be converted by the body into retinol are referred to as provitamin A carotenoids. Hundreds of different carotenoids are synthesized by plants, but only about 10% of them are provitamin A carotenoids.

VITAMIN A SOURCES

Different dietary sources of vitamin A have different potencies. For example, beta-carotene is less easily absorbed than retinol and must be converted to retinal and retinol by the body. One of the recent international standards of measure for vitamin A is retinol activity equivalent (RAE), which represents vitamin A activity as retinol. Two micrograms (mcg) of beta-carotene in oil provided as a supplement can be converted by the body to 1 mcg of retinol giving it an RAE ratio of 2:1. However, 12 mcg of beta-carotene from foods are required to provide the body with 1 mcg of retinol, giving dietary beta-carotene an RAE ratio of 12:1.

Retinol activity equivalents (RAE) ratios for beta-carotene and other provitamin A carotenoids

Quantity Consumed	Quantity Bioconverted to Retinol	RAE ratio
1 mcg of dietary or supplemental vitamin A	1 mcg of retinol*	1:1
2 mcg of supplemental beta-carotene	1 mcg of retinol	2:1
12 mcg of dietary beta-carotene	1 mcg of retinol	12:1
24 mcg of dietary alpha-carotene	1 mcg of retinol	24:1
24 mcg of dietary beta-cryptoxanthin	1 mcg of retinol	24:1

*One IU is equivalent to 0.3 microgram (mcg) of retinol, and one mcg of retinol is equivalent to 3.33 IU of retinol.

Food sources

Free retinol is not generally found in foods. Retinyl palmitate, a precursor and storage form of retinol, is found in foods from animals. Plants contain carotenoids, some of which are precursors for vitamin A (e.g., alpha-carotene, beta-carotene, and beta-cryptoxanthin). Yellow and orange vegetables contain significant quantities of carotenoids. Green vegetables also contain carotenoids, though the pigment is masked by the green pigment of chlorophyll [7]. A number of good food sources of vitamin A include cod liver oil, eggs, butter, milk, sweet potato, carrot, spinach and broccoli. Retinol activity of these foods comes mainly from provitamin A carotenoids

Supplements

The principal forms of preformed vitamin A (retinol) in supplements are retinyl palmitate and retinyl acetate. Beta-carotene is also a common source of vitamin A in supplements, and many supplements provide a combination of retinol and beta-carotene. Most multivitamin supplements available in the U.S. provide 1,500 mcg (5,000 IU) of vitamin A, which is substantially more than the current RDA for vitamin A. This is due to the fact that the Daily Values (DV) used by the FDA for supplement labeling are based on the RDA established in 1968 rather than the most recent RDA, and multivitamin supplements typically provide 100% of the DV for most

nutrients. Because retinol intakes of 5,000 IU/day may be associated with an increased risk of osteoporosis in older adults some companies have reduced the retinol content in their multivitamin supplements to 750 mcg (2,500 IU).

Vitamin A Signal Transduction and Regulation of Gene Expression

Vitamin A is provided either in lipid soluble form by animal-derived foods or in water-soluble form by plant-derived foods. Excess lipid-soluble vitamin A (preformed vitamin A) accumulates in body fat stores and in the liver and is associated with toxic effects. Conversely, excess water-soluble provitamin A (e.g., beta carotene) can be excreted and is usually not associated with toxic effects. The liver is the major site of storage and processing of vitamin A in the forms of retinyl esters and retinol, respectively. To meet tissue requirements, retinol is secreted from the liver, bound to the retinol binding protein, and transported through blood circulation toward the target organ.

Recently a membrane receptor was discovered with high affinity for retinol that is responsible for retinol uptake by cells. The tissue distribution of all-trans retinoic acid (RA) results from the balancing activities of cellular enzymes, including RA synthesizing retinaldehyde dehydrogenases and RA-catabolizing cytochrome P450 hydroxylases [(2)]. Once in the cell nucleus, the pleiotropic effects of RA are mediated through ligand-dependent transcriptional regulators belonging to the nuclear receptor superfamily: RA receptors (RARs) (α, β, and γ isotypes), which bind all-trans RA and its isomer 9-cis RA, and rexinoid receptors (RXRs) α, β, and γ isotypes), which bind 9-cis RA only.

As RAR/RXR heterodimers, these receptors control the transcription of RA target genes through binding to RA response elements. Animal- or plant-derived vitamin A derivatives are converted into all-trans RA (ATRA), which is the ligand of RA receptors (RARs) and rexinoid acid receptors (RXRs). In the absence of ATRA, the RXR/RAR heterodimers, bound to RA response elements (RAREs) on target genes, are associated with nuclear corepressors (NCoRs) and the transcription is inhibited, whereas in the presence of ATRA, nuclear coactivators (NCoAs) are recruited by RAR/RXR heterodimers and the transcription of target genes is activated.

A dimer is a complex of two protein molecules. Heterodimers are complexes of two different proteins, while homodimers are complexes of two of the same protein. Binding of all-trans-RA and 9-cis-RA to RAR and RXR respectively allows the complex to regulate the rate of gene transcription, thereby influencing the synthesis of certain proteins. RXR may also form heterodimers with thyroid hormone receptors (THR) or vitamin D receptors. In this way, vitamin A, thyroid hormone, and vitamin D may interact to influence gene transcription [(10, 14)]. Through the stimulation and inhibition of transcription of specific genes, retinoic acid plays a major role in cellular differentiation, the specialization of cells for highly specific physiological roles. Many of the physiological effects attributed to vitamin A appear to result from its role in cellular differentiation.

Role of vitamin A in regulation of physiological functions

Vision

The retina is located at the back of the eye. When light passes through the lens, it is sensed by the retina and converted to a nerve impulse for interpretation by the brain. Retinol is transported to the retina via the circulation and accumulates in retinal pigment epithelial cells. Here, retinol is esterified to form a retinyl ester, which can be stored. When needed, retinyl esters are broken apart (hydrolyzed) and isomerized to form 11-cis-retinol, which can be oxidized to form 11-cis-retinal. The latter can be shuttled across the interphotoreceptor matrix to the rod cell where it binds to a protein called opsin to form the visual pigment, rhodopsin (also known as visual purple). Rod cells with rhodopsin can detect very small amounts of light, making them important for night vision. Besides the biological formation of 11-cis retino, much attention has been given to the interaction of metarhodopsin II with a G-protein of the rod outer segment, termed transducin. This interaction sets a sequence of amplifying events leading to an electrical signal at the membrane of the rod outer segment .

Absorption of a photon of light catalyzes the isomerization of 11-cis-retinal to all-trans-retinal and results in its release. This isomerization triggers a cascade of events, leading to the generation of an electrical signal to the optic nerve. The nerve impulse generated by the optic nerve is conveyed to the brain where it can be interpreted as vision. Once released, all-trans retinal is converted to all-trans-retinol, which can be transported across the interphotoreceptor matrix to the retinal epithelial cell, thereby completing the visual cycle [(12)]. Inadequate retinol available to the retina results in impaired dark adaptation, known as "night blindness."

Immunity

Vitamin A is commonly known as the anti-infective vitamin, because it is required for normal functioning of the immune system [(15)]. The skin and mucosal cells (cells that line the airways, digestive tract, and urinary tract) function as a barrier and form the body's first line of defense against infection. Retinol and its metabolites are required to maintain the integrity and function of these cells. Vitamin A and retinoic acid (RA) play a central role in the development and differentiation of white blood cells, such as lymphocytes, which play critical roles in the immune response. Activation of T-lymphocytes, the major regulatory cells of the immune system, appears to require all-trans-RA binding of RAR [(14)].

Growth and development

Both vitamin A excess and deficiency are known to cause birth defects. Retinol and retinoic acid (RA) are essential for embryonic development [(15)]. During fetal development, RA functions in limb development and formation of the heart, eyes, and ears . Additionally, RA has been found to regulate expression of the gene for growth hormone.

Red blood cell production

Red blood cells, like all blood cells, are derived from precursor cells called stem cells. Stem cells are dependent on retinoids for normal differentiation into red blood cells. Additionally, vitamin A appears to facilitate the mobilization of iron from storage sites to the developing red blood cell for incorporation into hemoglobin, the oxygen carrier in red blood cells [11, 12].

Reduction of Mortality

Approximately a 30% reduction in child mortality results from supplements of vitamin A in areas in which vitamin A nutrients are generally inadequate. Large vitamin A supplements also tend to reduce the adverse effects of measles infections in malnourished populations [9].

Abnormal Vitamin A states and neurological disorders

Besides the teratogenic effects of vitamin A excess or deficiency during development, evidence accumulates to indicate involvement of the RA signaling pathway in several major CNS disorders described below.

Alzheimer disease: Retinoid signaling was implicated in Alzheimer disorder [6] because disturbed RA level is involved in amyloid plaque formation and evidence has been found linking late-onset Alzheimer disease and certain chromosomes which contain genes involved in RA signal transduction. Vitamin A has an antioxidant property that may explain its anti-amyloidogenic effect. Experimental evidence indicates that vitamin A deficiency results in accumulation of amyloid β- protein in cerebral cortex [3] and that such amyloid β- protein deposits can be cured by RA administration . Also, the blood level of vitamin A is reduced in patients with Alzheimer disease whereas expression of RA receptor α subtype (RARα) and of the RA-synthesizing enzyme retinaldehyde dehydrogenase is decreased in the cortex and meningeal vessels of postmortem Alzheimer disease brains [3].

Schizophrenia: Several lines of evidence suggest a link between the RA signaling pathway during development and schizophrenia which is considered to be related to neuro-developmental events resulting in ventricular enlargement and structural alteration in the frontal cortex, amygdala, hippocampus, temporal lobes, and cingulated gyrus. In addition, the dopaminergic system, which constitutes a well-documented pathway involved in schizophrenia and Parkinson disease [4] is one of the best-established targets of RA action in the CNS during development and adulthood [20]. The implication of retinoid signal transduction in controlling dopaminergic neurotransmission is strengthened by the presence of high levels of RA synthesizing enzymes in the mesotelencephalic dopamine system [17] and by the fact that RXR is believed to critically control the survival, adaptation, and homeostatic regulation of the dopaminergic system.

Depression: RA controls the differentiation of serotonergic neurons and the expression of serotonin$_{1A}$ receptors indicating a possible link between RA signal transduction and the serotonergic system, with implications for sleep and mood regulation. Excess vitamin A has been associated with depressive mood and sleep disorders.

Vitamin A Deficiency

Vitamin A deficiency and vision

Since the unique function of retinyl group is the light absorption in retinylidene protein, one of the earliest and specific manifestations of vitamin A deficiency is impaired vision, particularly in reduced light (night blindness). Vitamin A deficiency among children in developing nations is the leading preventable cause of blindness [19]. Persistent deficiency gives rise to a series of changes, the most devastating of which occur in the eyes. Some other ocular changes are referred to as xerophthalmia. First there is dryness of the conjunctiva (xerosis) as the normal lacrimal and mucus secreting epithelium is replaced by a keratinized epithelium. This is followed by the build-up of keratin debris in small opaque plaques (Bitot's spots) and, eventually, erosion of the roughened corneal surface with softening and destruction of the cornea (keratomalacia) and total blindness.

Vitamin A deficiency and infectious disease

The onset of infection reduces blood retinol levels very rapidly. This phenomenon is generally believed to be related to decreased synthesis of retinol binding protein (RBP) by the liver. In this manner, infection stimulates a vicious cycle, because inadequate vitamin A nutritional status is related to increased severity and likelihood of death from infectious disease. Vitamin A deficiency can be considered a nutritionally acquired immunodeficiency disease [13]. Even children who are only mildly deficient in vitamin A have a higher incidence of respiratory disease and diarrhea as well as a higher rate of mortality from infectious disease compared to children who consume sufficient vitamin A. Vitamin A supplementation has been found to decrease both the severity and incidence of deaths related to diarrhea and measles in developing countries, where vitamin A deficiency is common .

Other manifestations of deficiency

Other changes include hypokeratosis (white lumps at hair follicles), keratosis pilaris and squamous metaplasia of the epithelium lining the upper respiratory passages and urinary bladder to a keratinized epithelium. With relations to dentistry, a deficiency in Vitamin A leads to enamel hypoplasia. Adequate supply of Vitamin A is especially important for pregnant and breastfeeding women, since deficiencies cannot be compensated by postnatal supplementation.

Vitamin A Recommended Dietary Allowance (RDA)

The RDA for vitamin A was revised by the Food and Nutrition Board (FNB) of the Institute of Medicine in 2001. RDA is based on the amount needed to ensure adequate stores (four months) of vitamin A in the body to support normal reproductive function, immune function, gene expression, and vision. The table below lists the RDA values in both micrograms (mcg) of Retinol Activity Equivalents (RAE) and international units (IU).

Recommended Dietary Allowance (RDA) for Vitamin A as Preformed Vitamin A (Retinol Activity Equivalents)			
Life Stage	**Age**	**Males: mcg/day (IU/day)**	**Females: mcg/day (IU/day)**
Infants (AI)	0-6 months	400 (1,333 IU)	400 (1,333 IU)
Infants (AI)	7-12 months	500 (1,667 IU)	500 (1,667 IU)
Children	1-3 years	300 (1,000 IU)	300 (1,000 IU)
Children	4-8 years	400 (1,333 IU)	400 (1,333 IU)
Children	9-13 years	600 (2,000 IU)	600 (2,000 IU)
Adolescents	14-18 years	900 (3,000 IU)	700 (2,333 IU)
Adults	19 years and older	900 (3,000 IU)	700 (2,333 IU)
Pregnancy	18 years and younger	-	750 (2,500 IU)
Pregnancy	19 years and older	-	770 (2,567 IU)
Breast-feeding	18 years and younger	-	1,200 (4,000 IU)
Breast-feeding	19 years and older	-	1,300 (4,333 IU)

Protective role of retinoids in other cancers

Background: Carcinogenesis is a chronic and multistep process that converts normal cells into malignant cells. It probably results from mutagenic damage to growth-regulating genes and their products leading ultimately to development of invasive or metastatic cancers. Carcinogen exposure is hypothesized to form "fields" of altered cells long before invasive malignant disease is detected clinically. Once transformed, malignant cells acquire the ability to invade and metastasize, leading to clinically evident disease. During this continuum from normal to metastatic cells, carcinogenic steps can be arrested or reversed through pharmacological treatments, known as cancer chemoprevention. The process of chemoprevention should include interventions at the earliest stages of carcinogenesis, even before cancers are clinically apparent. If successful, this could avoid many clinical consequences of overt malignancy, as well as the need for treatment of disseminated malignancies that are often less responsive than early neoplastic lesions to therapeutic interventions.

Anti-neoplastic activity of retinoids

Retinoids i.e. naturally occurring and synthetic vitamin A (retinol) metabolites and analogs have been recognized as potent pharmacologic modulators of cell growth, differentiation and apoptosis. Cellular models and epidemiological data provide a strong rationale for the use of retinoids in cancer therapy and prevention. Furthermore, they have been shown to suppress carcinogenesis in various organs (e.g. oral cancer, skin, bladder, lung, prostate and breast cancers) in experimental animals [(12)].

Evidence for the retinoid role in cancer prevention was first provided in 1925 when vitamin A was reported as required for epithelial cell homeostasis. Rats rendered vitamin A-deficient developed squamous metaplasia at several epithelial sites, including the trachea. These tracheal metaplastic lesions were reminiscent of those found in smokers and were reversed following correction of the vitamin A deficiency. An additional link between vitamin A levels and incidence of neoplasia is found through epidemiological evidence showing an inverse relationship between vitamin A levels and incidence of specific malignancies.

These and other findings provided a basis for use of retinoids in clinical cancer prevention trials. Added support for a retinoid-based clinical chemopreventive approach stemmed from the successful retinoid treatment of premalignant lesions such as oral leukoplakia, xeroderma pigmentosum and cervical dysplasia. Clinical trials reveal that retinoids are active in reducing some second primary cancers. For example, 13-cis-retinoic acid (13-cRA) reduces second aero-digestive tract tumors in patients with resected head and neck cancers [(8)]. Second primary lung cancers are reduced by retinol palmitate treatment of patients following resection of stage I lung cancer. The acyclic retinoid, polyprenoic acid, inhibits second hepatocellular carcinomas after resection or ablation of primary liver cancer.

The above findings, when coupled with the single-agent activity of retinoids in treating overt malignancies, including acute promyelocytic leukemia, juvenile chronic myelogenous leukemia and mycosis fungoides, and the successful combination therapy with interferon-α-2A in the treatment of squamous cell carcinoma of the skin or cervix and in renal cancer provide support for a therapeutic role for the retinoids in the treatment of neoplastic disease. Evidence that 13-cRA is beneficial in the treatment of high-risk neuroblastoma after bone marrow transplantation indicates how the retinoids may have an adjuvant therapeutic role in the management of minimal residual disease in responding malignancies.

β -carotene in lung cancer prevention..conflicting results!

Numerous retrospective epidemiological studies have established an inverse relationship between dietary carotenoid levels and the incidence of specific cancers. Several animal and laboratory studies have substantiated β-carotene's ability to inhibit tumor cell growth and the progression of carcinogenesis. β -carotene could enhance lymphocyte proliferation independent of its pro-vitamin A function. It may exert an anti-carcinogenic action especially in the early stages of carcinogenesis.

Interestingly, however, studies in heavy smokers and in others that were at high risk for lung cancer (e.g. asbestos workers) showed that β-carotene supplementation unexpectedly increased lung cancer rates. More interestingly, a negative effect of beta-carotene supplementation has also been observed in experimental animals exposed to cigarette smoke [(21)].

Carotenoids, as a class, are particularly vulnerable to free radical attack due to their long chains of conjugated double bonds. A pro-oxidant effect has been seen in *in-vitro* and animal studies, both in high concentrations and in the presence of tocopherol deficiencies. The gas phase of cigarette smoke contains high levels of oxidants (nitric oxide) that have been shown to interact with lipid membranes to induce lipid peroxidation and protein oxidation to form protein-bound carbonyl groups [(5)]. The protein-carbonyl groups mediate inactivation of crucial enzymes such as creatine kinase and lecithin-cholesterol acyltransferase [(5)]. Carotenoids interact with cigarette smoke-containing oxidants. Depletion of carotenoids and tocopherol, particularly trans-β-carotene, alpha-tocopherol, and lycopene, has been demonstrated in cigarette smoke-exposed human plasma.

As β-carotene acts as a scavenger of nitrogen oxides in cigarette smoke, β-apo-carotenals and other carotene oxidation products are created that, if not effectively neutralized by other antioxidants (specifically tocopherol and ascorbate), may initiate cell damage that could lead to neoplasm . Multiple studies have substantiated that tocopherols (both alpha and gamma) protect carotenoids from auto-oxidation. Ascorbate also acts to protect both tocopherol and β-carotene from oxidative damage and has been shown to preserve β-carotene in oxidized human LDL.

The theory that β-carotene becomes an oxidant in the plasma and possibly tissues of smokers appears to be probable given the low antioxidant levels of smokers' blood. Nevertheless, whether or not these carotenoid radicals can initiate cancer is still disputed. **Baker *et al.*, 1999** [(1)] examined a model of liposomes exposed to cigarette smoke. They found that β-carotene neither enhanced lipid peroxidation in membranes nor contributed to the depletion of other antioxidants. They concluded that, although β-carotene is readily oxidized by smoke, pro-oxidant effects are unlikely to account for the apparent enhancement of lung cancer in smokers taking this supplement. However, recent studies suggest that the failure and harm seen in the chemoprevention trials with β-carotene against lung carcinoma could be explained by the pro-carcinogenic effect of the toxic oxidative carotene metabolites. The oxidative metabolites induce cytochrome P450 enzymes, lowering the serum levels of retinoid acid and down regulating retinoid receptors. On the other hand, nicotine by itself inhibits retinoid receptor expression via methylation.

Retinoids in Disease Treatment

Retinitis pigmentosa

Retinitis pigmentosa describes a broad spectrum of genetic disorders that result in progressive loss of photoreceptor cells (rods and cones) in the eye's retina. Early symptoms of retinitis pigmentosa include impaired dark adaptation and night blindness, followed by the progressive loss of peripheral and central vision over time. The results of a randomized controlled trial in more than 600 patients with common forms of retinitis pigmentosa indicated that supplementation with 4,500 mcg (15,000 IU)/day of preformed vitamin A (retinol) significantly slowed the loss of retinal function over a period of 4-6 years. In contrast, supplementation with 400 IU/day of vitamin E increased the loss of retinal function by a small but significant amount, suggesting that patients with common forms of retinitis pigmentosa may benefit from long-term vitamin A supplementation but should avoid vitamin E supplementation at levels higher than those found in a typical multivitamin. Up to 12 years of follow-up in these patients did not reveal any signs of liver toxicity as a result of excess vitamin A intake [(16)]. However, high-dose vitamin A supplementation to slow the course of retinitis pigmentosa requires medical supervision and must be discontinued if there is a possibility of pregnancy.

Acute promyelocytic leukemia

Normal differentiation of myeloid stem cells in the bone marrow gives rise to platelets, red blood cells, and white blood cells that are important for the immune response. Altered differentiation of those stem cells results in proliferation of immature leukemic cells, giving rise to leukemia. A mutation of the retinoic acid receptor (RAR) has been discovered in patients with a specific type of leukemia called acute promyelocytic leukemia (APL). Treatment with all-trans-retinoic acid or with high doses of all-trans-retinyl palmitate restores normal differentiation and leads to improvement in some APL patients [(12, 18)].

Diseases of the skin

Both natural and synthetic retinoids have been used as pharmacologic agents to treat disorders of the skin. Etretinate and acitretin are retinoids that have been useful in the treatment of psoriasis, while tretinoin (Retin-A) and isotretinoin (Accutane) have been used successfully to treat severe acne. Retinoids most likely affect the transcription of skin growth factors and their receptors [(12)].

SUMMARY AND CONCLUSIONS

Vitamin A is an essential micronutrient whose role in visual function has been known for thousands of years. The role vitamin A plays in basic physiologic processes, such as growth, reproduction, immunity, and epithelial tissue maintenance, has been also known for a long time. Although vitamin A is essential throughout the entire life span, yet its influence is particularly critical during periods when cells proliferate rapidly and differentiate, such as during pregnancy and early childhood. Vitamin A and its precursors are available in several food items as well as in commercial preparations. Actions of vitamin A have been shown to be mediated through binding to particular nuclear receptors that regulate synthesis and physiological functions of different hormones. This process may also be facilitated through transport of the vitamin by certain plasma binding proteins.

Deficiency of vitamin A may be associated with serious health problems such as night blindness, reduced immunity, increased risk of respiratory infections and hematological disorders. Such health problems can be successfully managed through the use pharmacological preparations of vitamin A or fortification of diet with

vitamin A rich foods. On the other hand, chronic overuse of the vitamin may lead to more serious disorders especially affecting the bone and central nervous system; and may even precipitate birth defects. Furthermore, interactions of vitamin A with certain drugs especially alcohol and nutrients may result in either vitamin deficiencies or risk of toxicities particularly affecting the liver and the lung tissues. Therefore, in spite of the undeniable role of vitamin A in maintenance of healthy bodily functions, yet the use of this particular vitamin should be optimized to achieve the best prophylactic and therapeutic goals and, in the meantime, avoid serious adverse consequences.

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