Vitamin A

Vitamin A (VA) is an essential micronutrient that plays an important role in a wide array of physiologic processes, including vision, immune response, cell differentiation and proliferation, intercellular communication, and reproduction. By definition, VA refers to the fat-soluble compound all-*trans*-retinol. However, it is commonly used to collectively represent retinol and its active metabolites, including retinal, retinyl ester, and retinoic acid. Retinoic acid regulates the transcription of >500 genes involved in cell growth and differentiation by serving as the natural ligand for α, β, and γ retinoic acid and retinoid X receptors. The aldehyde derivate of VA, 11-*cis*-retinal, serves as a chromophore in the photoreceptor cells of the retina. The photoisomerization of 11-*cis*-retinal to all-*trans*-retinal activates a signaling cascade that results in the perception of light in vertebrates. Consequently, one of the clinical manifestations of vitamin A deficiency (VAD) in humans is severe night blindness or xerophthalmia. Retinyl esters such as retinyl palmitate do not have a documented biological function directly but serve as storage forms of VA and as a substrate for the formation of active metabolites of VA.

Humans and animals must obtain VA from the diet or through supplemental sources. These sources are primarily derived from animal products that provide preformed VA (retinol or retinyl esters consumed as preformed VA or converted from pro-VA carotenoids) or from fruits and vegetables as sources of pro-VA carotenoids. Carotenoids, a class of lipophilic hydrocarbons, are secondary plant metabolites responsible for the red, yellow, and orange pigments in plants and some micro-organisms. Although >600 carotenoids exist in nature, pro-VA activity is limited to those possessing ≥1 β-ionone ring along with the polyene chain, including β-carotene, α-carotene, and β-cryptoxanthin. Theoretically, the metabolism of β-carotene would yield 2 molecules of retinol because β-carotene possesses 2 β-ionone rings, whereas α-carotene and β-cryptoxanthin would have half the pro-VA activity of β-carotene by virtue of their structure containing only one β-ionone ring.

Deficiencies

VAD results primarily from inadequate VA intake. VAD is one of the most prevalent nutrition-related health problems, with 190 million preschool-aged children characterized by biochemical VA deficiency (defined as low serum retinol concentration) and 5 million preschool-aged children suffering from night blindness worldwide (1). The classic manifestation of VAD is xerophthalmia, which is a disorder related to dryness of the eye. Xerophthalmia results in a range of ocular expressions of VAD, from night blindness, conjunctival, and corneal xerosis to corneal ulceration and keratomalacia which ultimately lead to blindness if left untreated (1). Other major health consequences of VAD include severely reduced immune competence, which leads to an increased susceptibility to infectious diseases and a higher risk of mortality, particularly in children and lactating women (1). Serum retinol, serum retinol–binding protein, and breast-milk retinol have been used to identify populations at risk for VAD. However, there are limitations in using these biomarkers to determine the VA status of individuals. Specifically, serum concentration of retinol is homeostatically regulated and remains constant under a wide range of VA intake or liver stores. Thus, a substantial decrease in serum retinol concentration may not be apparent unless liver reserves of VA are dangerously low. In addition, factors such as acute-phase response to infection and inflammation, pregnancy, and other micronutrient deficiencies affect circulating retinol concentrations. Although relatively costly and more labor-intensive, the assessment of VA liver stores with the use of isotope dilution methodology is considered the most reliable and noninvasive measure of VA status. A liver VA store of 0.07 μmol/g has been used as a cutoff for VAD based on an estimated protection from the physiologic symptoms of VAD (1).

Dietary Recommendations

The Institute of Medicine (IOM) Estimated Average Requirement for VA is calculated based on the amount of dietary VA required to maintain adequate VA liver stores at 0.07 μmol/g (2). The WHO and FAO have proposed values for VA intake based on a composite of indicators of VAD (3, 4). Because VA can be supplied by pro-VA carotenoids, retinol activity equivalents (RAEs) and retinol equivalents (REs) are used by the IOM and FAO, respectively, to equate different sources to retinol, where 1 μg RAE is equivalent to 1 μg retinol, 12 μg β-carotene, or 24 μg α-carotene or β-cryptoxanthin (2) and 1 μg RE is equivalent to 1 μg retinol, 6 μg β-carotene, or 12 μg α-carotene or β-cryptoxanthin (3). The difference in these equivalencies reflects different levels of confidence in updated absorption data. The IOM RDA is 300 μg RAEs/d for children aged 1–3 y, 750 μg RAEs/d for adult women, and 900 μg RAEs/d for adult men (2). Similarly, WHO and FAO guidelines recommend a daily VA intake of 400 μg REs for children aged 1–3 y, 500 μg REs for adult women, and 600 μg REs for adult men (4).

Food Sources

The richest sources of preformed VA in the US diet include liver, eggs, and fortified dairy and cereal products (~50–3300 μg RAEs/100 g). High concentrations of pro-VA carotenoids can be found in yellow and orange vegetables (e.g., carrots, sweet potatoes, and pumpkins), yellow and orange noncitrus fruits (e.g., mangos, apricots, and papayas), and dark-green leafy vegetables (e.g., kale, spinach, and collards)

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(~20–900 μg RAEs/100 g) (3). In countries in which VAD is a public health problem, the fortification of staple foods is used for the widespread delivery of VA. These foods include sugar, flours from wheat or maize, vegetable oil, and fortified products such as the peanut butter paste intended to combat general severe malnutrition.

Clinical Uses

The prophylactic supplementation of VA has been widely used in VA-deficient populations, and current WHO guidelines recommend that the prophylactic oral administration of VA supplements be given to children aged 6–59 mo in regions in which VA has been recognized as a public health problem (5). The suggested dose is a single supplement of 100,000 IU (30 mg RAEs) VA for infants aged 6–11 mo and 200,000 IU (60 mg RAEs) VA for children aged 12–59 mo every 4–6 mo because VA can be stored in the liver and mobilized as needed. VA as all-*trans*-retinoic acid is used to treat acute promyelocytic leukemia; the dose is given as 45 mg $\cdot$ m^{-2} $\cdot$ d^{-1} orally in combination with anthracycline-based chemotherapy and is considered the standard of care for this type of cancer (6). VA as retinyl palmitate at doses of 5000 μg RAEs/d has been used to slow the progression of retinitis pigmentosa, a genetic disorder characterized by the breakdown of the retina, although its efficacy in slowing the disease is not universally accepted (7).

Toxicity

VA toxicity generally occurs after chronic intakes >10,000–15,000 μg RAEs/d because of the long half-life of VA in the body. Toxicity symptoms include dry skin, headaches, anorexia, nausea, bone pain, and cerebral edema. Acute toxicity has also been observed after the ingestion of very high doses. The current Tolerable Upper Intake Level (UL) for preformed VA is 3000 μg/d for adults (1). No UL exists for carotenoids because high carotenoid intake has not been observed to result in toxicity symptoms, likely because of the relatively lower absorption efficiency of carotenoids as well as the regulation of the β-carotene conversion to VA by VA status and dose size.

The ULs were established based on reports that have demonstrated adverse health consequences of the chronic consumption of preformed VA leading to teratogenicity and liver abnormalities. Excess preformed VA intake has also been associated with lower bone mineral density leading to an increased risk of osteoporosis and bone fracture; however, findings remain conflicting and not thoroughly conclusive.

VA intake in most developed countries often exceeds the RDA or even the UL for most age groups, but the levels are usually below the no-observed-adverse-effect level. In the United States, the 95th percentile of VA consumption from foods and supplements by nonpregnant women aged 19–30 y as well as preschool-aged children exceeds the UL but not the no-observed-adverse-effect level of these age groups (8).

Recent Research

Despite the recognition of the prevalence of VAD for decades, the most effective approaches for addressing the problem are still under investigation. Recent research includes studies on methods for biofortifying staple foods to create sustainable strategies for at-risk populations and those on the effect of these biofortified crops, such as cassava and maize, on the VA status of children in various populations. There is also increasing awareness that vulnerable populations may receive multiple forms of supplementation, potentially resulting in hypervitaminosis A, and studies for improving biomarkers to identify this condition are underway. Relating to both VAD and toxicity, there is currently a significant effort underway to better understand the equilibration of recently ingested VA with body stores to improve isotope dilution protocols and strategies for assessing exposure and status after VA interventions (9). Specific to VA function, several studies are investigating the molecular mechanisms behind the potential chemopreventive and protective properties of VA in different diseases and conditions. Mechanisms of retinoic acid signaling in different morphogenesis is also being explored. There is also a growing international collaboration to address VAD by generating new food-processing methods to enhance the bioavailablity of pro-VA carotenoids from plant sources. Current studies are also investigating methodologies to establish appropriate conversion factors for estimating the bioavailable VA content of plant foods.

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Abbreviations used: IOM, Institute of Medicine; RAE, retinol activity equivalent; RE, retinol equivalent; UL, Tolerable Upper Intake Level; VA, vitamin A; VAD, vitamin A deficiency.

References

1. WHO. Global prevalence of vitamin A deficiency in populations at risk, 1995–2005, WHO global database on vitamin A deficiency. Geneva (Switzerland): WHO; 2009.
2. National Academy of Sciences. Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington (DC): National Academy Press; 2001.
3. WHO. Human vitamin and mineral requirements. Rome (Italy): FAO; 2001.
4. WHO. Vitamin and mineral requirements in human nutrition. 2nd ed. Geneva (Switzerland): WHO; 2004.
5. WHO. Guideline: vitamin A supplementation in infants and children 6–59 months of age. Geneva (Switzerland): WHO; 2011.
6. Lo-Coco F, Cicconi L, Breccia M. Current standard treatment of adult acute promyelocytic leukaemia. Br J Haematol 2016;172: 841–54.
7. Sacchetti, M., Mantelli, F, Merlo, D, Lambiase A. Systematic review of randomized clinical trials on safety and efficacy of pharmacological and nonpharmacological treatments for retinitis pigmentosa. J Ophthalmol 2015;2015:737053.
8. Allen LH, Haskell M. Estimating the potential for vitamin A toxicity in women and young children. J Nutr 2002;132:2907S–19S.
9. Ford JL, Green JB, Green MH. Should we restrict vitamin A intake, a minor contributor to plasma retinol turnover, when using retinol isotope dilution equations to estimate an individual's vitamin A status, or should vitamin A balance be maintained? J Nutr 2017; 147:1483–6.