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The Double-Edged Sword of Vitamin A: Function and Toxicity

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ABSTRACT

Introduction: This article investigates the essential functions and health risks of vitamin A, focusing on its metabolic pathways, dietary origins, daily requirements, the clinical consequences of deficiency and the harmful effects of overdose.

Materials and Methods: A thorough literature search was performed using PubMed and Google Scholar databases with the following keywords: "Vitamin A", "retinoids", "vitamin A deficiency", "hypervitaminosis A", "retinoic acid", "immune function", "vision", "skin health", "toxicity", and "wound healing".

Summary: Vitamin A is a fat-soluble micronutrient essential for maintaining healthy vision, a strong immune system, proper growth, reproduction, and skin integrity. It is found in two main forms: preformed vitamin A and provitamin A carotenoids. After intestinal absorption, it is primarily stored in the liver and converted into active compounds such as retinoic acid, which regulate gene expression and support epithelial health and immune function. Deficiency can result in night blindness, increased susceptibility to infections, delayed wound healing, and skin disorders. On the other hand, excessive intake, particularly from supplements, may lead to acute or chronic toxicity affecting the liver, bones, and nervous system, and can be harmful during early pregnancy due to its teratogenic effects. Ensuring adequate vitamin A intake is therefore key to supporting overall health.

Conclusions: Vitamin A is essential for human health, but both its deficiency and excess pose significant risks. Deficiency remains a major concern in low-income countries, while preventing toxicity is increasingly important in high-income populations due to widespread supplement use. Key strategies include education, nutritional screening, food fortification, and individualized supplementation. Further research is needed to define safe dosage limits and therapeutic uses, particularly for vulnerable groups like pregnant women and children.

Keywords: "Vitamin A", "retinol", "retinoic acid", "deficiency", "hypervitaminosis A", "toxicity", "vision", "supplementation", "teratogenicity"

Introduction

Vitamin A (VA) is a fat-soluble nutrient that is essential for numerous physiological functions, playing a vital role not only in supporting cellular growth and differentiation but also in regulating various metabolic processes. Additionally, it is crucial for maintaining a healthy immune system, ensuring proper eyesight by contributing to the visual cycle, and supporting

reproductive health and development [1]. Vitamin A is formally defined as the fat-soluble compound all-trans-retinol. However, the term is often used more broadly to encompass retinol and its active metabolites, including retinal, retinyl esters and retinoic acid [2]. Vitamin A is defined by an unsaturated isoprenoid chain structure. All its isoforms exhibit a similar molecular architecture and perform analogous functions within the organism. All of these compounds are lipophilic and, unlike water-soluble vitamins, can be readily stored in the body, primarily in the liver and adipose tissue. Animal-based foods are rich in the retinyl ester form of vitamin A, while fruits and vegetables predominantly contain carotenoids, the majority of which act as provitamin A [3]. Dietary retinyl esters and carotenoids are absorbed by intestinal enterocytes, where they undergo esterification and are subsequently incorporated into chylomicrons. These large lipoprotein complexes are secreted into the lymphatic and circulatory systems, where they are metabolized into chylomicron remnants that are efficiently taken up by the liver and peripheral tissues. Within the liver, the majority of vitamin A is stored as retinyl esters in hepatic stellate cells. Upon physiological demand, these stores are mobilized through hydrolysis to release retinol, which circulates bound to retinol-binding protein 4 (RBP4) and transthyretin (TTR), facilitating its delivery to target organs. Retinol transport between hepatic stellate cells and hepatocytes is tightly regulated, with retinoic acid serving as a key modulator of lipogenic processes within hepatocytes. Vitamin A is an essential micronutrient involved in a wide range of biological functions, notably in cellular differentiation, embryonic development, and the regulation of immune responses. Deficiency in vitamin A is most commonly linked to a range of health impairments, including significant problems with vision, deterioration of skin health, compromised bone growth and remodeling and a weakened immune system [4].

Sources of Vitamin A

Preformed vitamin A is predominantly present in high concentrations within animal-derived foods, with the richest sources including liver, various types of fish, eggs, and dairy products. The primary dietary sources of provitamin A carotenoids encompass a wide variety of plant-based foods, notably including leafy green vegetables, vibrant orange and yellow vegetables, tomato-based products, various types of fruits and certain selected vegetable oils. Additionally, vitamin A is commonly added to various fortified foods, including milk, margarine and certain

ready-to-eat breakfast cereals. Sweet potatoes, spinach, and carrots are particularly rich in provitamin A carotenoids [5].

Tab. 1. Foods with the highest vitamin A content

Food	Microgram per serving
Beef liver	6,582
Sweet potato	1,403
Spinach	573
Pumpkin pie	488
Carrot	459
Herring	219

Requirements

The Institute of Medicine establishes the Recommended Dietary Allowance (RDA) for vitamin A at 700 µg/day for adult women and 900 µg/day for adult men. The daily requirements for VA differ significantly depending on the stage of life and physiological conditions. For example, children typically require an intake ranging from 300 and 900 µg/day to support their growth and development. Pregnant women have an increased need, with recommended amounts around 770 µg/day, to ensure proper fetal development and maternal health. This demand is further elevated during lactation, where women may require up to 1300 µg/day. In children aged 1 to 5 years, a minimum daily intake of approximately 200 µg is sufficient to prevent the clinical manifestations of vitamin A deficiency (VAD). The

concentration of retinol in the serum is widely regarded as a dependable indicator for evaluating an individual's vitamin A status, as levels falling below 20 μg/dL are typically interpreted as a clear sign of VA deficiency [1].

The Role of Vitamin A

Vitamin A constitutes a class of lipophilic compounds essential for human homeostasis, with critical involvement in visual physiology, T-cell mediated immunomodulation, and a broad spectrum of other biological systems. VA is fundamental not only for maintaining corneal integrity but also for retinal function, serving as the biochemical precursor of the visual chromophore 11-cis-retinal. This chromophore is indispensable for phototransduction within photoreceptor cells and undergoes continuous regeneration via a tightly regulated series of enzymatic reactions collectively termed the visual cycle, which involves the retinal pigment epithelium and Müller glial cells [6].

Vitamin A plays a vital role in the immune system by exerting significant immunomodulatory effects that impact both innate and adaptive immune responses, thereby strengthening the body's defense mechanisms and enhancing overall host resistance to a diverse range of infectious pathogens [7]. Retinoic acid (RA), the biologically active derivative of vitamin A, is critically involved in regulating immune function. It directs lymphocyte migration to the gastrointestinal tract and other mucosal surfaces, supports the synthesis of immunoglobulin A (IgA), and governs the differentiation of key T cell subsets, including regulatory T cells (Tregs), Th17 cells, and the polarization of Th1 and Th2 responses [8]. Both provitamin A carotenoids and preformed vitamin A contribute to the mitigation of oxidative stress within the body, though they operate via distinct mechanisms. Carotenoids function as direct antioxidants by neutralizing reactive oxygen species, whereas vitamin A exerts its effects indirectly by modulating the expression of genes involved in the endogenous antioxidant defense system [9]. VA plays a protective role in infectious disease outcomes, with evidence indicating its efficacy in lowering both morbidity and mortality rates in conditions such as measles, childhood diarrheal illnesses, malaria, and hand, foot and mouth disease [10].

Retinoids are crucial in regulating the growth and differentiation of multiple skin cell types, with their deficiency leading to aberrant epithelial keratinization. In the context of tissue injury, vitamin A enhances epidermal turnover, accelerates re-epithelialization, and restores the integrity of the epithelial structure [11]. Retinoic acid plays a crucial and multifaceted role

in the regulation of hair follicle biology, as it is deeply involved in the stimulation of hair growth, promotion of proper cellular differentiation within the follicular environment, and the initiation and support of hair follicle regeneration mechanisms essential for maintaining healthy hair cycles [12]. In clinical dermatology, a broad spectrum of therapeutic agents comprises retinoids - bioactive derivatives of vitamin A - such as tretinoin, isotretinoin, alitretinoin, acitretin, adapalene, tazarotene, bexarotene and trifarotene. These compounds are extensively employed in the treatment of conditions like acne and psoriasis due to their potent anti-inflammatory effects and their ability to modulate epidermal cell proliferation, differentiation and sebaceous gland activity [13]. Topical retinoids have been extensively documented to induce histological and clinical improvements in photoaged skin, including enhancement of epidermal and dermal thickness, refinement of skin surface texture and attenuation of fine rhytides [14]

Deficiency

Vitamin A deficiency (VAD) remains the primary cause of preventable childhood blindness globally, although it is largely considered eliminated in high-income countries. However, specific at-risk populations persist, including children with autism spectrum disorder, who may exhibit an increased susceptibility to VAD [15]. In industrialized nations, disorders affecting the pancreas, liver and intestines represent the primary etiologies of vitamin A deficiency. Similar to the recurrent gastrointestinal infections prevalent in low-resource settings, inflammatory bowel disease (IBD) causes sustained intestinal mucosal inflammation which, when accompanied by inadequate nutritional intake, can result in vitamin A depletion [10]. Additionally, various forms of chronic liver disease have been implicated in the development of vitamin A deficiency [1]. Deficiency of vitamin A results in widespread disruption of mucosal epithelial integrity across various organ systems, including the ocular surface, oropharynx, respiratory passages, gastrointestinal tract and genitourinary epithelium [16]. Vitamin A deficiency in the retina initially compromises rod photoreceptor function, resulting in night blindness. Subsequently, cone photoreceptors become affected, leading to impaired photopic vision and reduced visual acuity. The delayed onset of cone dysfunction is thought to result from an alternative pathway for 11-cis-retinal synthesis mediated by Müller glial cells [17]. Night blindness serves as one of the earliest and most sensitive clinical signs indicating marginal vitamin A deficiency, often manifesting before more severe symptoms

develop [16]. VAD manifests through numerous clinical signs, notably xerophthalmia, which involves conjunctival dryness, thickening, and loss of transparency [18]. Insufficient levels of vitamin A have been implicated in the exacerbation of numerous infectious diseases, dysbiosis, and a compromised immune response to vaccination [17]. Infection elevates the physiological requirement for vitamin A, thereby exacerbating the existing deficiency [19]. Vitamin A has been recognized as an essential and critical factor in promoting the proliferation and regeneration of epidermal cells, especially in the context of cutaneous infections. Consequently, vitamin A deficiency may manifest as dermatologic irritation or compromised skin integrity. Furthermore, vitamin A facilitates the biosynthesis of collagen, a structural protein integral to dermal architecture and essential for the wound healing process. Experimental studies in both rodent models and human subjects have demonstrated that VAD is associated with impaired wound healing, whereas vitamin A supplementation has been shown to enhance tissue repair and, in some cases, prevent the onset of cutaneous lesions [20]. Follicular hyperkeratosis emerges as a consequence of vitamin A deficiency and is effectively ameliorated through the administration of high-dose vitamin A therapy [21],

Adverse effects

Acute vitamin A toxicity can arise following a single ingestion of vitamin A at doses equal to or exceeding 25,000 IU per kilogram of body weight. Clinical manifestations typically include gastrointestinal disturbances such as nausea, vomiting, and diarrhea, along with neurological symptoms like dizziness, lethargy, somnolence, and signs of increased intracranial pressure. Dermatological effects may also be observed, including erythema, pruritus and desquamation. Chronic vitamin A toxicity may develop as a consequence of consistently consuming 4000 IU per kilogram or more of vitamin A each day over a period ranging from 6 to 15 months [22]. Toxicity symptoms associated with chronic vitamin A exposure commonly include xerosis, alopecia, brittle nails, fatigue, anorexia, musculoskeletal pain and hepatomegaly. Chronic retinoid toxicity exerts multisystem effects, with especially pronounced effects on the skeletal system. It can result in the formation of bone spurs, abnormal calcification of soft tissues and an accelerated breakdown of bone tissue. These alterations disrupt normal bone metabolism, potentially causing elevated blood calcium levels (hypercalcemia), decreased bone mineral density, and an increased likelihood of fractures, particularly in the hip region, thereby significantly compromising bone strength and overall

skeletal integrity. Neurological involvement in certain conditions can manifest through a variety of symptoms, including persistent headaches, feelings of nausea and episodes of emesis (vomiting) [22]. Vitamin A exhibits teratogenic properties as demonstrated in multiple animal species, with the nature of the malformations contingent upon both the dosage of vitamin A and the specific gestational period during which administration occurs. Considering the established teratogenic effects of vitamin A in animal models and isotretinoin in humans, vitamin A (excluding beta-carotene) is recognized as teratogenic, particularly during the initial 60 days post-conception in humans [23].

Summary

Vitamin A is a vital fat-soluble nutrient that plays a central role in maintaining numerous physiological functions, including cellular growth, immune system regulation, reproduction, skin integrity, and, most notably, vision. It comprises a group of compounds such as retinol, retinal, retinyl esters, and retinoic acid, all of which share similar molecular structures and are stored primarily in the liver. Vitamin A can be obtained from dietary sources in two main forms: preformed vitamin A from animal-based foods like liver, eggs, and dairy products, and provitamin A carotenoids from plant-based foods such as leafy greens, carrots, and sweet potatoes. The bioavailability and metabolism of these forms differ but ultimately contribute to the body's vitamin A pool. The recommended dietary intake of vitamin A varies depending on age, sex and physiological states such as pregnancy and lactation. Maintaining adequate vitamin A levels is crucial, as deficiency can lead to a spectrum of serious health problems. These include visual impairments such as night blindness and xerophthalmia, increased susceptibility to infections due to impaired immune responses, poor epithelial and skin health, delayed wound healing, and in severe cases, preventable childhood blindness. Although vitamin A deficiency is now rare in high-income countries, it remains prevalent in low-resource settings and among vulnerable populations, including children with certain medical conditions. Conversely, excessive intake of vitamin A, particularly through supplements or high-dose therapy, can lead to acute or chronic toxicity. Symptoms of toxicity range from gastrointestinal disturbances and neurological symptoms to dermatological changes and skeletal abnormalities. Chronic toxicity can also cause teratogenic effects if exposure occurs during early pregnancy, highlighting the importance of cautious use during this period. While vitamin A deficiency remains a major public health concern in low-resource settings,

overconsumption - particularly through supplementation - can result in serious toxicity. The duality of its effects highlights the need for individualized dietary strategies and public health interventions that ensure adequate intake without exceeding safe upper limits. Continued education, monitoring, and tailored nutritional programs are essential to optimize vitamin A status globally, balancing its indispensable benefits with the risks associated with improper intake.

Disclosure

Author's contribution

Conceptualization: Magdalena Jabłonowska

Methodology: Magdalena Jabłonowska

Formal analysis: Paulina Grzeszczuk

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