Vitamin A

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Introduction

Vitamin A is a vital, but often ignored, nutrient for health optimization and disease prevention. Vitamin A is important to the prevention of cancer, night blindness, and infection. More than 50 percent of Americans do not meet the daily requirement of Vitamin A intake while other Americans ingest excess Vitamin A from supplements, which increases risk of Vitamin A toxicity, birth defects, and osteoporosis. The daily ingestion of Vitamin A is a delicate balancing act between ingesting enough Vitamin A to derive its beneficial effects, while at the same time avoiding over ingestion of this nutrient. This article highlights the important physiological and clinical aspects of Vitamin A that health practitioners should be aware of in regards to making recommendations to their patients about optimizing Vitamin A status and the use of supplements containing Vitamin A.

General Features

Preformed Vitamin A is a fat-soluble group of related compounds. The most common preformed version present in food is retinol; others are retinal (retinaldehyde), and retinoic acid. Retinol can be reversibly oxidized to retinal, which is required for night vision. Oxidation of retinal produces retinoic acid, which does not participate in the visual cycle and cannot be converted back to the aldehyde form (retinal). However, retinoic acid does support growth and normal differentiation of epithelial tissue, but does not support reproductive function, as do other forms of Vitamin A.

In general Vitamin A serves at least five major functions in the body: (1) It helps cells reproduce normally and undergo complete differentiation to fully developed adult cells (cells that have not properly differentiated are more likely to undergo pre-cancerous changes). (2) It is required for vision and one of the first symptoms of Vitamin A deficiency is night blindness. (3) It is required for normal growth and development of the embryo and fetus, influencing genes that determine the sequential development of organs in embryonic development. (4) It may be required for normal reproductive function, with influences on the function and development of sperm, ovaries and placenta. (5) It is a powerful fat-soluble antioxidant. Vitamin A is vital to health optimization and health maintenance as studies show that Vitamin A-deprived animals not only go blind, but also die shortly thereafter. Due to its diverse effects on epithelial cells, including growth, replication, differentiation and antioxidant function, animal studies have shown that Vitamin A reduces the risk of cancer development in epithelial cells in the presence of certain carcinogens.

Absorption and Metabolism

Preformed Vitamin A is absorbed in the gastro-intestinal tract, enters the lymphatic system, within chylomicrons and then the general circulation, which ultimately delivers Vitamin A to the liver, the main storage site (90%) for Vitamin A (also stored to a lesser degree in the

kidneys, adipose tissue, and adrenal glands). It is released from the liver in the form of retinol, bound to retinol-binding protein (RBP).

80-90 percent of Vitamin A is typically absorbed from the gut demonstrating excellent bioavailability. Retinoic acid from food is absorbed from the gut and transported in the blood bound to albumin. It normally does not accumulate within the liver or other tissues in any appreciable amounts.

Once delivered to the cells via the bloodstream Vitamin A is extracted from the bloodstream and binds to intracellular proteins within the cell known as CRBP (cellular retinal-binding protein) and CRABP (cellular retinoic acid-binding protein). Within the cells of the body Vitamin A modulates many biochemical reactions, which promote growth, replication, differentiation, and provides additional antioxidant protection.

Functions

1. **Vision**

   Within the retina, the 11-cis isomer of Vitamin A aldehyde (retinal) is combined with the protein opsin (rhodopsin in the rods and iodopsin in the cones). Light changes the 11-cis configuration to the all-trans form of retinal. This causes visual excitation. When there is a deficiency of Vitamin A, the rods and cones cannot adjust to light changes and night blindness is an early consequence when these cells, especially the rods, are deprived of Vitamin A.

2. **Growth and Bone Development**

   Through its effects on protein synthesis and differentiation, Vitamin A is necessary for growth and development of bones and soft tissues. It is also required for enamel-forming epithelial cells in the development of teeth. Retinoic acid appears to be the most important form of Vitamin A for these purposes.

3. **Epithelial cell and mucous membrane development and maintenance**

   Retinoic acid is required for the development of mucous epithelial cells that line the respiratory tract, the alimentary canal, and the urinary tract. Vitamin A deficiency results in “keratinizaton” (drying and hardening) of these tissues, which lowers the protective barrier of these tissues against infection. Sub-optimal Vitamin A status may also render these tissues more susceptible to cancerous changes.

4. **Immune Function**

   Vitamin A influences both humoral and cell-mediated immunity. The circulating number of T lymphocytes as well as their response to mitogens is reduced in Vitamin A deficiency. Vitamin A is also known as the anti-infective vitamin due to its effects on mucous membranes, helping to create a barrier to infection.

5. **Reproduction**

   Animal studies provide evidence that retinal is required for normal reproduction and lactation.

6. **Antioxidant**

   Vitamin A is a potent fat-soluble antioxidant, which appears to have important implications in regards to the prevention of epithelial cancers.

Retinol Equivalents (RE): In addition to preformed Vitamin A, which is present in animal foods, orange-yellow fruits and vegetables and dark green vegetables contain precursors to Vitamin A synthesis, which occurs in the body (e.g. Beta-carotene). In North America, approximately fifty percent of Vitamin A is derived from Vitamin A precursors from the consumption of fruits and vegetables. The following chart outlines the retinal equivalent values of various carotenes as well as preformed Vitamin A.

1 Retinol equivalent	=	1 ug. Retinal
	=	6 ug. Beta-Carotene
	=	12 ug. other provitamin A carotenoids
	=	3.33 I.U. Vitamin A activity from retinol
	=	10 I.U. Vitamin A activity from Beta-Carotene

Recommended Daily Allowance

Group	
Adult males	1,000 Retinol Equivalents (RE)
Adult women	800 RE or 4,000 IU
Pregnancy	1,000 RE (5,000 IU)
Lactation	1,200 RE (2,000-5,000 IU)
Children	400-1,000 RE (2,000-5,000 IU), the amount increasing from infancy to 14 years.

Overt Deficiency of Vitamin A

1. **Night Blindness (Nyctalopia)**
2. **Xerophthalmia or Xerosis Conjunctivae**

This progressive disorder of the eye leading to blindness involving dryness, thickening, wrinkling and pigmentation of the conjunctiva, Bitot's spots, dryness and keratinisation of the cornea and finally ulceration, softening of the cornea and possibly perforation and iris prolapse and infection.

3. **Follicular Hyperkeratosis (Toad Skin)**

Goose flesh appearance known as Xeroderma. In follicular hyperkeratosis, the hair follicles are blocked with plugs of keratin from the epithelial lining. The result is rough, dry, scaly skin beginning with the forearms and thighs and progressing to full-body involvement.

4. **Other:**
   a. growth inhibition
   b. skeletal abnormalities
   c. decreased resistance to infection
   d. taste bud keratinisation and loss of sense of taste
   e. loss of appetite[1]

The North American Vitamin A Status Update

The National Health and Nutrition Examine Surveys (I and II), along with the Continuing Survey of Food Intakes by Individuals and 1994-96 Diet and Health Knowledge Survey (ARS Food Surveys Research Group. Internet – 1997), indicate that approximately 56 percent of Americans do not meet the daily requirement for Vitamin A intake. In fact, in many cases individuals only consume 50% of the RDA level on a daily basis. Thus, marginal deficiency of Vitamin A is not uncommon in developed countries. As such, the use of a multiple vitamin supplement each day providing 2,500-3,000 IU of preformed Vitamin A and 10,000-15,000 IU of beta-carotene may be highly beneficial to health optimization and the prevention of epithelial cancers according to epidemiological studies, and experimental data. However, consuming a multiple vitamin containing 5,000 IU or more of preformed Vitamin A, may increase risk of Vitamin A toxicity over the long-term, increase risk of osteoporosis in postmenopausal women, and may increase risk of birth defects. On the other hand, there are special cases where higher doses of Vitamin A can be used on a therapeutic basis, but higher doses require proper monitoring for Vitamin A toxicity and should not be used during pregnancy, lactation or by individuals with liver or kidney disease.

Vitamin A Toxicity

Toxicity has been associated with abuse of Vitamin A supplements and with diets extremely high in preformed Vitamin A. Consumption of 25,000-50,000 IU/d for periods of several months or more can produce multiple adverse effects. Individuals at highest risk have liver function previously comprised by drugs, viral hepatitis, alcohol, or protein-energy malnutrition.

Children - adverse effect have been shown to occur with intakes as low as 1,500 IU/kg/day.

Pregnant women - increased risk of birth defects has occurred with maternal intakes as low as 25,000 IU/day.

From a clinical standpoint, Vitamin A toxicity typically occurs in patients taking high dose Vitamin A (≥ 50,000 IU) for various skin conditions (e.g. acne, psoriasis, eczema). Even synthetic water-soluble Vitamin A has been shown to cause toxicity at doses of 18,500 to 60,000 IU per day over a period of months.

Signs and Symptoms of Vitamin A Toxicity	
Children	Adults
Anorexia Bulging fontanelles Drowsiness Increased intracranial pressure Irritability Vomiting	Abdominal pain Anorexia Blurred vision Drowsiness Headache Hypercalcenia Irritability Muscle weakness Nausea, vomiting Peripheral neuritis Skin desquamation Brittle nails

	Cheilosis Gingivitis Alopecia

Birth defects associated with high maternal intake of Vitamin A (18,000-100,000 IU before and throughout pregnancy):

Abnormalities of the head, face, ears, eyes, mouth, lips, jaw, heart and urinary system: other defects[2]

Dosages greater than 10,000 IU during pregnancy (specifically the first 7 weeks after conception) have probably been responsible for one out of 57 cases of birth defects in the United States. Women who are at risk for becoming pregnant should keep their supplemented Vitamin A levels below 5,000 IU per day.[3] A study showed that 59 women taking prescription Vitamin A 13-cis retinoic acid (Accutane) for acne, who became pregnant resulted in 12 spontaneous abortions and 21 malformed infants.

Vitamin A Supplementation

1. **Acute Viral Infection 50,000 IU for one or two days**

2. **Cancer Treatment and Prevention**

   Wolback and Howe noted that retinoid-deficient epithelial tissues had a premalignant phenotype (appearance) that was characterized by enhanced mitotic activity (rapid cell turnover) and loss of differentiation.4

   Retinoids are known to possess antiproliferative, differentiative, immunomodulatory and apoptosis-inducing properties. A growing body of evidence supports the hypotheses that the retinoic acid receptor B2 gene is a tumor suppressor gene, and that the chemopreventive effects of retinoids are due to induction of this receptor.5 A unique Vitamin A compound is presently being used in cancer prevention and treatment. This form of Vitamin A, known as 9-cis-retinoic acid, has been used to suppress premalignant oral lesions and prevent the development of secondary primary cancers among patients with head and neck and lung cancers. This form of Vitamin A is now being considered in the treatment of breast cancer, which often displays under expression of the retinoic acid receptor B2.6-9

   Note that a number of alternative practitioners and holistic medical practitioners often recommend high doses of water soluble Vitamin A (50,000-300,000 IU per day) as part of the adjunctive nutritional support for patients with certain cancers. Many of these practitioners suggest it is a useful intervention to help prevent recurrence of certain cancers and control the spread of existing lesions (www.diagnoseme.com). In these cases, monitoring for Vitamin A toxicity is mandatory.

3. **Acne**

There is some evidence that Vitamin A supplementation at 25,000 IU per day may improve acne. However, this dose may lead to signs of toxicity (headache, cracking and chapped lips, fatigue, dry skin, and joint pain are early warning signs and symptoms). A dose above 5,000 IU per day also increases the risk of birth defects in children born to mothers ingesting these higher levels of Vitamin A at the time of conception.[10]

In my experience, a safer and more appropriate natural treatment for acne is the ingestion of the P73 Wild Oregano Capsules in conjunction with topical application overnight of the P73 Wild Oregano Cream. This form of wild oregano has been shown to kill many bacteria, viruses and fungi, which appears to include the bacteria involved in acne.

Drug-Nutrient Interactions

1. Bile acid sequestrants such as cholestyramine and colestipol, are known to reduce Vitamin A absorption.[11,12]
2. Neomycin is known to reduce the absorption of Vitamin A and increase its excretion, which increases need for Vitamin A supplemention.[13]
3. Mineral oil decreases the absorption of Vitamin A.[14]
4. Vitamin A-derivative drugs (isotretinoin) may increase risk of toxicity by potentiating the effects of Vitamin A. Caution should be exercised with respect to Vitamin A supplementation in these cases.[15]
5. Orlistat decreases Vitamin A levels in the body which increases demand for Vitamin A supplementation.[16,17]
6. Corticosteroid drugs may decrease Vitamin A levels in the body, which increases demand for Vitamin A supplementation.[18]
7. High doses of Vitamin A may impair the absorption of Vitamin E if taken concurrently.[19]

Pregnancy and Lactation

During pregnancy and lactation, the only supplements that are considered safe include standard prenatal vitamin and mineral supplements. All other supplements or dose alterations may pose a threat to the developing fetus and there is generally insufficient evidence at this time to determine an absolute level of safety for most dietary supplements other than a prenatal supplement. Any supplementation practices beyond a prenatal supplement should involve the cooperation of the attending physician (eg., magnesium and the treatment of preeclampsia.)

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