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OVERVIEW OF VITAMIN A

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Abstract

Vitamin A is a fat-soluble vitamin that is important for many bodily functions, including proper vision, a strong immune system, reproduction and good skin health. There are two types of vitamin A found in foods: preformed vitamin A and provitamin A. It is also known as retinol and commonly found in meat, fish, eggs and dairy products. Besides, body converts carotenoids in plant foods, such as red, green, yellow and orange fruits and vegetables, into vitamin A.

But, many people in developing countries do not get enough Vitamin A. The highest risk of vitamin A deficiency is in pregnant women, breastfeeding mothers, infants and children. Signs and symptoms of vitamin A deficiency could be dry skin, dry eyes, night blindness, male and female infertility and trouble conceiving, delayed growth, throat and chest infections, poor wound healing, acne and breakouts, cystic fibrosis and chronic diarrhea. However, hypervitaminosis A, excess vitamin A, or vitamin A toxicity causes serious vision changes, mouth ulcers, confusion and birth defects.

Key words: Vitamin A, Sources, Deficiency, Blindness, Growth, Toxicity, Overview.

Introduction

Vitamins are a number of chemically unrelated families of organic substances that cannot be synthesized by humans and must be ingested in diet in small quantities to facilitate normal metabolism. They are divided into water-soluble and fat-soluble vitamins (Tab. 1).

Ancient Egyptians recognized that night blindness could be treated by consumption of liver (Wolf, 1996). von Hubbenet (1860) associated between night blindness and a corneal defect, followed by conjunctival xerosis with foamy white spots on the cornea now known as (Bitot's spots) as a strong clinical indicator of vitamin A deficiency, which is usually reversible with vitamin A supplementation (Bitot, 1863). Walker *et al.* (1982) suggested that bone abnormalities in fossilized skeletal remains of early humans were caused by excessive preformed vitamin A intakes. McLaren (1981) reported that in the past Vitamin A was known as "luxus" vitamin, and that excessive intake habitually exists among some per-sons, reinforced the point that maintaining balance was important for overall health. Later Karrer *et al.* (1931) stated that the fat-soluble compound in liver was isolated and termed vitamin.

Review and Discussion

Chemistry: Vitamin A is a subclass of a family of lipid-soluble compounds referred to as retinoic acids. These consist of four isoprenoid units joined in a head to tail fashion. Two forms of vitamin A are available in the human diet: preformed vitamin A (retinol and its esterified form, retinyl ester) and provitamin A carotenoids (Johnson and Russell, 2010). The hypothesis that higher dietary β-carotene intake and serum level results in higher β-carotene-mediated signaling was partly questioned. Alternative autoregulatory mechanisms in β-carotene/ retinoidmediated signaling are highlighted to better predict and optimize nutritional strategies involving β-carotene-related health beneficial mediated effects (Bohn *et al,* 2019). Provitamins A are many forms but beta-carotene is the only one metabolized by mammals into vitamin A (Rougereau *et al,* 1987).

Preformed vitamin A (all-trans-retinol and its esters) and provitamin A (beta-carotene) are essential dietary nutrients that provide a source of retinol. Both retinol esters and beta-carotene are metabolized to retinol (Dawson, 2000).

Sources: vitamin A is found in foods from animal sources, including dairy products, fi-

sh, and meat (especially liver). The most important provitamin A carotenoid is beta-carotene; other provitamin A carotenoids are alpha-carotene and beta-cryptoxanthin. Provitamin A (beta-carotene) is mostly found in green leafy vegetables, sweet potato and carrots. Because vitamin A from animal sources or supplements is preformed, it is more likely to cause toxicity than the provitamin A from plant sources. Both must be metabolized intracellularly to retinal and retinoic acid, the active forms of vitamin A, to support the vitamin's important biological functions (Ross, 2006).

Metabolism: The initial steps in metabolism depend on the type of vitamin A ingested. The metabolism of provitamin A (beta-carotene) into active vitamin A is a highly regulated step (Conaway *et al,* 2013).

Provitamin A (mostly beta-carotene of plant sources), must be cleaved to retinal before absorption. This step is subject to feedback regulation, which depends on vitamin A status.

Preformed vitamin A (retinol, retinal, retinoic acid, and retinol esters, from supplements or animal sources) is hydrolyzed into retinol in the lumen of the small intestine. A number of retinol ester hydrolases are involved in this process at the level of the mucosal brush-border (Harrison, 1993). It also appears that pancreatic enzymes have a role in retinoid assimilation. Bile salts form micelles which allow water solubilization of the products of lipolysis and absorption through the intestinal mucosa. These steps are highly efficient and not subject to feedback regulation (Rigtrup and Ong, 1992). Within the small intestine, retinols are re-esterified into retinol-esters, incorporated into chylomicrons, and excreted into lymphatics and plasma (Chen *et al,* 2003).

In the blood, chylomicrons are then broken down into multiple remnants including apolipo-proteins B & E, which contain retinol esters (Ross and Owusu, 2017). Apolipoproteins are then taken up by the liver via a receptor-mediated endocytosis on the surface of the hepatocytes, and the retinol esters are released, which further metabolized to eventually combine with Retinol Binding

Proteins (RBP) before storage in vitamin A-containing lipid globules within hepatic stellate cells; formerly known as Ito cells (Ross, 2000). About 50 to 85% of the total body retinol is stored in the liver and also in many other tissues in much smaller concentrations. In order for vitamin A to reach its target organs, it binds to RBP molecules for release into plasma as a retinol-RBP complex (Green *et al,* 1988).

Actions: Vitamin A has a number of biologic actions.

Vision: In eye, vitamin A has two major roles; prevention of xerophthalmia (abnormalities in corneal and conjunctival development) and photo-transduction. Two types of retinal photoreceptor cells are involved in the visual process. The cone cells are responsible for the absorption of light and color vision in bright light. The rod cells detect motion and are responsible for night-vision. In the rod cells of the retina, all-trans-retinol is converted to 11-cis-retinol, which then combines with a membrane-bound protein called opsin to yield rhodopsin. A similar type of reaction occurs in the cone cells of the retina to produce iodopsin. In man scot opic sensitivity matches the absorption spectrum of rhodopsin; but photopic sensitivity, when not distorted by the yellow pigmentations of lens and macula lutea lies at shorter wave lengths than iodopsin (Wald *et al,* 1955).

The visual pigments absorb light at different wavelengths depending upon the type of cone cells. As an example, the red-sensitive cone cells absorb any light stimulus in the wavelength of the color red. This leads to the absorption of three basic colors, red, green, and blue. Light-activated transformation of these complexes leads to a cascade of hyperpolarization of rod cell membrane, thus enabling the transmission of light stimuli to the CNS (Saari, 1994).

Cellular differentiation: Other than its importance in vision, vitamin A is crucial to

cellular differentiation and integrity in the eye. All the cells in the conjunctiva and the retina have RBPs, suggesting the dependence of these tissues on retinoic acid. Normal fetal development of eye also requires adequate vitamin A intake and stores. A number of studies in vitamin A depleted animals showed abnormal fetal eye tissue development (Sommer and West, 1996).

Deficiency: Vitamin A deficiency was rare in the United States and other industrialized countries. But, it was still the third most common nutritional deficiency worldwide (Williams, 1997). In a large part of the third world (Southern and Southeast Asia, Africa, and South America), night blindness, complete blindness and advanced stages of xerophthalmia occur in many malnourished children and adults (Janczewska *et al,* 1995). This represents a major public health problem; about 500,000 preschool-children become blind each year and many die (Underwood and Arthur, 1996). Routine distribution of vitamin A to children in endemic areas prevents these ophthalmic complications (Katz *et al*, 1995), and has other important benefits: In a meta-analysis of 43 randomized controlled trials conducted in low- and mid-income countries, vitamin A supplementation given to children between six months and five years of age was associated with a 24% reduction in all-cause mortality and a 28% reduction in diarrhea-associated mortality (Mayo-Wilson *et al*, 2011). Also, Vitamin A supplementation to children in undernourished populations reduces longterm risk of hearing loss among those with ear discharge; a marker for otitis (Schmitz *et al,* 2012). Chabra *et al.* (2013) suggested Vitamin A supplementation (VAS) to prevent bronchopulmonary dysplasia. Gadhia *et al*. (2014) reported that only 1 of 4 studies showed a significant reduction in BPD incidence associated with vitamin A supplementation (in conjunction with iNO). Schwartz *et al.* (2017) reviewed these results and suggested that IM vitamin A might have a modest benefit in reducing BPD risk among preterm infants. They added that more studies must assess infant groups, which were most likely to benefit from supplementation (based on birth weight or other conditions) and optimal dose.

Vitamin A deficiency with or without xerophthalmia were seen in patients with disorders associated with fat malabsorption, such as cystic fibrosis, celiac disease, cholesteric liver disease such as primary biliary cirrhosis, small bowel Crohn's disease, and pancreatic insufficiency; xerophthalmia also was reported in the developed world in individuals with extremely limited diets due to mental health disorders (Lin *et al,* 2011).

Measurement: The diagnosis of vitamin A deficiency is usually made by clinical findings, but can be supported by serum retinol measurement levels less than 20mg/dl, or the ratio of retinol: RBP a molar ratio <0.8 suggested deficiency (de Pee and Dary, 2002). Serum carotene levels correlated with vitamin A status, and low serum carotene can be used as a surrogate marker of malabsorption and nutritional status.

Serum vitamin A concentrations do not reflect total vitamin A stores under certain conditions: Serum retinol levels may be artificially low (i.e., underestimate vitamin A stores) in the setting of severe protein-calorie malnutrition because dietary protein, energy and zinc are required for synthesis of retinol binding protein (RBP). Also, serum retinol levels may be low during undercurrent infection because of transient decreases in negative acute phase proteins including RBP. Conversely, in a patient with vitamin A deficiency, a dose of vitamin A may cause a transient rise in serum retinol concentrations, leading to overestimation of the patient's vitamin A stores (Feingold *et al,* 2000).

Clinical manifestations: 1- Xerophthalmia describes a spectrum of eye disease caused by vitamin A deficiency. It is characterized by pathologic dryness of the conjunctiva and cornea, caused by inadequate function of the lacrimal glands and is manifested by Bitot's spots (areas of abnormal squamous cell pro-

liferation and keratinization of conjunctiva), progressing to corneal xerosis (dryness) and keratomalacia (Morgan and Weinsier, 1998). Vitamin A deficiency also causes night blindness (nyctalopia) and retinopathy because vitamin A is a substrate for the photo-sensitive visual pigments in the retina. Vitamin A deficiency is known for its adverse health consequences, such as blindness, growth retardation and death Thus, working on maternal health need to focus on mothers with low incomes in order to reduce their deficiency in Vitamin A (Baytekus *et al,* 2019). 2- Poor bone growth. Vitamin A and retinoid derivatives are recognized as morphogens that govern body patterning and skeletogenesis, producing profound defects when in excess. In post-natal bone, both high and low levels of vitamin A are associated with poor bone heath and elevated risk of fractures (Green *et al,* 2016). 3- Non-specific dermatological problems, such as hyperkeratosis, phrynoderma (follicular hyperkeratosis), and destruction of hair follicles and their replacement with mucus-secreting glands (Morriss-Kay and Sokolova, 1996). 4- Impairment of the humoral and cell mediated immune system via direct and indirect effects on phagocytes and T cells (Cantorna *et al,* 1995). Supplementation with vitamin A at the community level in developing countries was recommended by the WHO because of its beneficial effects on immunity (Cantorna *et al,* 1996).

Vitamin A in disease prevention: People commonly inquire about vitamin and mineral supplementation and diet as a means to prevent or manage dermatological diseases and, in particular, hair loss. Answering these queries is frequently challenging, given the enormous and conflicting body of evidence that exists on this subject (Bronsnick *et al,* 2014). The latest findings promote new evidence-based recommendations to prevent, and treat atopic dermatitis, psoriasis, acne, and skin cancer highlighted the requirement for more researches (Murzaku *et al,* 2014). Almohanna *et al.* (2019) reported that vitamins and minerals in the hair cycle and immune defense mechanism have a marked role; large double-blind placebo-controlled trials were required to determine the effect of specific micronutrient supplementation on hair growth in those with both micronutrient deficiency, and non-scarring alopecia to establish any association between hair loss and such micronutrient deficiency. Vitamin A deficiency was common among populations in developing countries (WHO, 1997).

Periodic distribution: To prevent clinical vitamin A deficiency in populations, vitamin A supplements can be distributed at four to six month intervals at the following doses, where 1 microgram retinol=3.3 International units (IU): a- Infants <6 months of age, b- Non breast-fed: 50,000 IU orally, c- Breast fed: 50,000 IU orally (unless mother received supplemental vitamin A), d- Infants 6 to 12 months of age: 100,000 IU orally, e- Children >12 months of age: 200,000 IU orally, and f- Mothers: 200,000 IU orally within eight weeks of delivery (Tab. 2).

Vitamin A replacement women should not be high-dose supplements because of potential teratogenic effects, but they must receive frequent small doses not exceeding 10,000 IU daily or 25,000 IU weekly (Darlow *et al,* 2016).

High-dose supplementation: For children at high risk of vitamin A deficiency, such as those with measles, diarrhea, respiratory disease, or severe malnutrition, who live among populations at risk for vitamin A deficiency, and have not, received supplements within the past 1 to 4 months, WHO recommended a single dose of vitamin A at the age-specific dose (Lopez *et al,* 2006).

Xerophthalmia: For treatment of xerophthalmia, vitamin A is given in three doses at the age-specific doses. The first dose is given immediately on diagnosis, the second on the following day, and the third dose at least two weeks later. Women of reproductive age or who are pregnant and have night blindness should be treated with frequent small doses of vitamin A. Xerophthalmia patients should be treated with same high dose sche-

dule as adults (WHO, 2009). Vitamin A deficiency during pregnancy increases risk of maternal night blindness and anemia and may be a cause of congenital malformation (Cañete *et al,* 2017)

Excess: The majority of the vitamin A toxicity cases are due to the chronic ingestion of large amounts of synthetic (or preformed) vitamin A i.e., about 10 times more than the Recommended Dietary Allowance (RDA), or about 50,000 IU (Biesalski, 1989). Water-miscible, emulsified, and solid forms of retinol supplements, which include those in candy-like supplements marketed for children, are more toxic than oil-based preparations (Myhre *et al,* 2003).

Individuals who ingest large amounts of provitamin A (from plant sources) may develop yellow-tinged skin (carotenemia) without developing vitamin A toxicity. Carotenemia is particularly common among infants and toddlers who are eating large amounts of pureed vegetables (particularly carrots and green leafy vegetables), and may be initially confused with jaundice. The skin discoloration resolves spontaneously if the intake of these foods is reduced. Less commonly, carotenemia may also be caused by some diseases, including nephrosis, diabetes mellitus, anorexia nervosa, liver disease, and hypothyroidism, due to decreased conversion of beta carotene into retinol (Weber *et al,* 1982). Carotenemia is yellow pigmentation of skin (xanthoderma) and increased beta-carotene levels in the blood. In many cases, it followed prolonged or excessive consumption of carotene-rich foods, such as carrots, squash, and sweet potatoes. Carotenemia is harmless common finding in children, but may be a mistaken diagnosis with jaundice, and may have a significant symbolic significance (Hisao and Clukay, 2017).

Three syndromes of vitamin A toxicity have been recognized: acute, chronic, and teratogenic. Large supplemental doses of retinol are very toxic to the liver, but due to large storage capacity of the liver for vitamin A, the actual toxic doses are not well established (Weber *et al,* 1982).

Treatment of vitamin A toxicity consists of stopping vitamin A supplements and restricting vitamin A-rich foods (especially sources of preformed vitamin A, such as liver, kidney and egg yolk). If the patient has evidence of hepatotoxicity or pseudotumor cerebri, supportive treatment is indicated. Most case reports of chronic toxicity suggested gradual resolution of the symptoms after vitamin A withdrawal, although hepatic fibrosis persisted (Guarascio *et al,* 1983).

Acute toxicity: Acute toxicity occurs in adults when a single dose of >660,000 IU (>200,000 micrograms) of ingested vitamin A. Symptoms include nausea, vomiting, vertigo, and blurry vision. In very high doses, drowsiness, malaise, and recurrent vomiting can follow the initial symptoms listed above. In infants under six months of age, as little as 20,000 IU (6000 micrograms) given briefly (e.g., for one month or less) produced toxic effects (Olson, 1999).

Chronic toxicity: Chronic toxicity occurs with long-term ingestion of vitamin A doses in amounts higher than 10 times the RDA i.e., toxicity may occur with chronic ingestion of about 33,000 IU [10,000 micro-grams] of retinol in adults (Sibulesky *et al,* 1999). Some toxic effects of vitamin A were also reported in infants fed large amounts of chicken liver containing 300 IU (90mg retinol) for one month or longer (Mahoney *et al,* 1980). Signs of chronic toxicity include ataxia, alopecia, hyperlipidemia, hepatotoxicity, bone & muscle pain, visual impairments, and many other non-specific signs, and symptoms (Lam *et al,* 2006).

Because most vitamin A is stored in the liver, circulating serum levels of vitamin A (retinol) are not helpful in diagnosing vitamin A toxicity. Patients with hypervitaminosis A may have low, normal, or high serum levels of retinol, depending on the timing, quantity, and form of vitamin A ingested, and patient's age (Cheruvattath *et al,* 2006).

Serum retinol esters in the fasting state are sometimes used as a marker for chronic hyp-

ervitaminosis A; retinol ester concentrations >10% of the total vitamin A pool was considered abnormal i.e., a molar ratio of plasma retinol esters to the sum of plasma retinol and retinol esters (Smith and Goodman, 1976). However, this ratio may still not reflect hepatic stores long after the toxic ingestion has stopped. Elevated serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and/or calcium were reported (Krasinski *et al,* 1989).

Symptoms and signs of toxicity include dry skin, nausea, headache, fatigue, irritability, hepatomegaly, alopecia, hyperostosis, and increased cerebrospinal fluid pressure (pseudo-tumor cerebri). Although children with cystic fibrosis are at risk for fat-soluble vitamin deficiency due to their pancreatic insufficiency, standard supplementation regimens may lead to excessive levels of vitamin A. In one study, children with CF who were given standard supplements, total vitamin A intake and serum retinol values were elevated, raising concerns about the possibility of chronic toxicity which may contribute to CF-associated liver and bone disease (Graham-Maar *et al,* 2006).

Hepatotoxicity can lead to cirrhosis and associated with veno-occlusive disease. A prominent histologic finding is the proliferation of hepatic stellate cells. Several factors can increase the toxicity of vitamin A, including underlying liver and kidney disease, alcoholism, and the use of some drugs, such as tetracyclines (Penniston and Tanumihardjo, 2006).

Adverse effects on bone: There is some evidence that intake levels of vitamin A in the high-normal range may have adverse effects on bone health. In a prospective cohort study of postmenopausal women, long-term intake of a diet high in retinol (vitamin A) was associated with an increased risk of osteoporotic fractures (Feskanich *et al,* 2002). Similarly, high serum retinol levels were associated with an increased fracture risk in men (Michaëlsson_*et al,* 2003). Thus, high doses of vitamin A may compromise bone health, but the threshold at which clinically relevant effects are seen remains to be determined (Crandall, 2004).

Many drugs can affect bone metabolism (Wolinsky-Friedland, 1995): 1- heparin causes bone loss by decreasing bone formation or increasing bone resorption (Muir *et al,* 1996), 2- Warfarin decreases the tendency of blood to clot by inhibiting vitamin K-dependent gamma-carboxylation of clotting factors II, VII, IX, & X (Hirsh, 1991). 3- Cyclosporine adversely affects bone, administration to rats caused an increase in both bone resorption and bone loss, or high-turnover osteoporosis (Bryer *et al,* 1995). 4- Glucocorticoids are the most effective anti-inflammatory drugs used to treat patients with airways disease These act on virtually all cells within the airway to suppress airway inflammation or prevent recruitment of inflammatory cells into the airway and many mechanisms related to inflammation were responsible for the failure of these patients to res-pond correctly to GCs and these provide in-sight into GC actions within the airways (Adcock and Mumby, 2017). 5- Medroxyprogesterone acetate (MPA, Provera) low doses (5 to 10mg/day) used in combination with estrogen as part of a regimen of postmenopausal hormone therapy have no effect on the ability of estrogen to prevent bone loss, cancer drugs and thyroid hormone can cause bone loss, while thiazide diuretics can minimize bone loss (Cundy *et al,* 1996). 6- Cancer drugs, most cases of osteoporosis in treated patients were due to either hypogonadism resulted from chemotherapy and radiation therapy, from blockade of estrogen synthesis with aromatase inhibitors, or to glucocorticoid therapy (Pfeilschifter and Diel, 2000). Cancer drugs improvement in prostate cancer survival over time, even in those with advanced disease, led to an increasing recognition of the impact of prostate cancer and its treatment on bone health (El Badri *et al,* 2019). 7- Thyroid hormones are essential for skeletal development and important regulators of bone maintenance in adults and in chi-

ldhood hypothyroidism causes delayed skeletal development, retarded linear growth and impaired bone mineral accrual. Besides, subclinical hyperthyroidism is associated with low bone mineral density (BMD) and an increased risk of fracture (Williams and Bassett, 2018). 8- Thiazide diuretics act more distally, increase tubular calcium reabsorption, provide protection against hypercalciuria, and may raise serum calcium, suppress PTH secretion and improve bone metabolism (Alon, 2018). Loop diuretics increase calciuria that reduce bone mineral density and increase vertebral fracture risk, but rarely cause hyponatremia. Long-term thiazide therapy was associated with a less risk of low-energy fractures (Taipale *et al,* 2019).

Teratogenic effects: Retinoic acid has been known to be very teratogenic in first trimester of pregnancy led to spontaneous abortions and fetal malformations as microcephaly and cardiac anomalies. Effects may occur at doses only several times the RDA (Rothman *et al,* 1995). Many animal models as well as human studies have shown high incidence of birth defects in mothers who ingested therapeutic doses of retinoic acid for dermatological uses (Soprano and Soprano, 1995). A safe upper limit for vitamin A intake during pregnancy was recognized at about 10,000 IU daily about 3000 micrograms (Imdad *et al,* 2010).

Vitamin A-associated effects are completed mainly via all trans retinoic acid (ATRA), which targets a wide range of nuclear receptors include retinoic acid receptor (RAR), retinoid X receptor (RXR), and peroxisome proliferator-activated receptor (PPARβ/δ), where polymorphic retinoic acid (RA) response elements able to activate the kinase cascades; assimilated in nucleus via phosphorylation of RA signaling effectors (Al Tanoury *et al,* 2013) The nuclear receptors targeted by ATRA have a role in oral cancer and was able to restore gap junctional intercellular communication for oral cancer cells by Cx32 & Cx43 upregulation (Wang *et al,* 2013). Retinoic acid amide inhibited the JAK-STAT pathway in lung cancer, leading to apoptosis (Li *et al,* 2015). Retinoic acid receptor (RAR) promoter methylation can be used as a predictive diagnostic marker for non-small cell lung cancer (Feng *et al,* 2016). The hypermethylation of RAR promoter was associated with other known factors that influence lung cancer; one of the most important factors is cigarette smoke. On the other hand, the therapeutic induced hypomethylation of RAR promoter by using curcumin could be a possible anti-cancer therapy (Jiang *et al,* 2015)

Therapeutic uses: Retinoic acid and carotenoids have several therapeutic uses.

Measles: Vitamin A treatment of children with measles infection in developing countries reduced complications and mortality and in selected circumstances in developed countries (Huiming *et al,* 2005).

Dermatology: Retinoic acid has been used for many hyperkeratotic and hyperproliferative disorders of skin. Synthetic oxidative metabolites of vitamin A such as isotretinoin capsule can be used topically or systemically for treatment of a variety of skin disorders. Systemic forms have been used in some forms of psoriasis and other disorders of keratinization and even skin cancer. 13-cis-retinoic acid reduces the proliferation of sebaceous glands, and due to such properties it is used for treatment of acne and acne-related disorders. Some of the conjugated forms of retinoic acids (i.e., retinol beta-glucuronide) were used as topical creams or ointments for hyperpigmentation or for reducing wrinkling associated with sun exposure (Orfanos *et al,* 1997).

Atherosclerosis: Because carotenoids are antioxidants, they were investigated for possible prevention of cardiovascular disease. But, randomized trials of vitamin A and beta-carotene have no benefit for primary or secondary prevention of coronary heart disease; besides, there is some evidence that its supplementation increased mortality from cardiovascular disease and may increase risk of lung and colon cancer. Thus, in industria-

lized countries where dietary intake of vitamin A is generally adequate, supplementing with vitamin A for disease prevention is not recommended. Kadri *et al.* (2020) studied the effect of vitamin A & D combination supplement on interleukin-1β (IL-1β) and clinical outcome in ischemic stroke. They concluded that combination of vitamin A & D supplementation significantly increased vitamin A & D serum level, decreased IL-1β serum level, and ultimately improved clinical outcome in ischemic stroke patients.

Acute promyelocytic leukemia: All-trans-retinoic acid (ATRA or tretinoin) is a synthetic oxidative metabolite of retinoic acid used in acute promyelocytic leukemia (a subgroup of acute myelocytic leukemia (Degos and Wang, 2001). Initial studies showed a remarkable response to high-dose daily treatment with all-trans-retinoic acid, about 45 mg/m2/day. But, later study showed that such high doses can lead to a dangerous condition known as the differentiation syndrome (retinoic acid syndrome) characterized by respiratory distress, fevers, kidney failure, and hypotension. Because a large number of patients died, the drug was administered for short periods of time, in conjunction with other standard chemotherapy (Chomienne *et al*, 1996). Stahl and Tallman, (2019) reported that acute promyelocytic leukemia differentiation syndrome (APL DS) resulted when patients with APL were treated with all-trans retinoic acid (ATRA) and/or arsenic trioxide (ATO). They added that immediate treatment with steroids at the first clinical suspicion was recommended and ATRA/ATO should be stopped in severe cases or if no response, and that the utility of steroid prophylaxis in order to prevent APL DS was less certain.

General population requirements: Recommended daily allowance (RDA) for vitamin A as retinol activity equivalents (RAE), where one RAE = 1 microgram retinol or 3.3 IU. RDA for adult males is 3000 IU (900micrograms retinol) daily, & for females 2300 IU (700 micrograms retinol) daily.

Special populations' requirements: Individuals with clinically significant fat malabsorption due to pancreatic insufficiency or other digestive disorders are at risk for deficiency of vitamin A and other fat-soluble vitamins. Patients with cystic fibrosis were routinely treated with supplements of fat-soluble vitamins which provide doses that are several folds higher than the RDA. Daniels and Davidson (1989) reported that malnutrition gave a negative impact on pulmonary function in children with cystic fibrosis. In the past, dietary management has aimed at high energy low fat intake, but showed to fall far short of the 120-150% of recommended daily allowance for energy cystic fibrosis patients require. The nutritional management included a high energy, high fat containing diet, high carbohydrate intake; high salt intake; replacement of fat-soluble vitamins; appropriate use of pancreatic enzyme preparations; and supplemental feeding when indicated children and adolescents with cystic fibrosis frequently have growth failure by combination of malabsorption, increased energy needs with reduced appetite. Nutrient delivery and correction of maldigestion and malabsorption achieved normal growth to support optimal pulmonary function and prolong life (Borowitz *et al*, 2005). Ratchford *et al.* (2018) reported that cystic fibrosis is a severe, progressive, multisystemic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator gene. Optimizing nutrition is critical, as higher growth parameters are associated with better pulmonary function and outcomes, but unfortunately patients with this disease are prone to malnutrition, growth failure, and vitamin deficiencies.

Individuals with chronic liver disease are typically treated with a standard multivitamin which includes vitamin A. If vitamin A deficiency is detected in these patients, standard replacement doses should be given. High levels of alcohol consumption appear to potentiate the hepatotoxic effects of vitamin A (Leo and Lieber, 1999). Individuals

with marked cholestasis may require higher doses of vitamin A and other fat-soluble vitamins in order to maintain adequate levels. Children with cholesteric liver disease often require between 5,000 and 25,000 IU (1500-7500 micrograms retinol) daily of water-miscible vitamin A (Feranchak *et al,* 2005). For patients treated with these high doses of vitamin A, monitoring for clinical or laboratory evidence of vitamin A toxicity (usually assayed as serum retinyl esters in fasting state) was recommended (Feranchak and Sokol, 2007). Freund and Gotthardt (2017) reported that chronic cholestatic diseases are progressive diseases of biliary tract that cause hepatic fibrosis and liver failure, and that vitamin A deficiencies caused chronic cholestasis and retinoid metabolism attenuated or even prevented hepatic fibrosis. Lee (2018) in liver cirrhotic patient reported that malnutrition was due to poor oral intake, maldigestion, malabsorption associated renal disease, and metabolic abnormalities, and thus check the dietary intake and body composition as anthropometry, and muscle functions. Veraldi *et al.* (2020) reported that children affected with chronic liver disease were at risk for fat-soluble vitamins deficiency, and that liver transplant was effective to improve vitamin A & E, but not affect vitamin D. A consensus was needed to define optimal nutritional management of these patients in order to prevent deficiencies.

Conclusion

Vitamin A is a subclass of a family of lipid-soluble compounds referred to as retinoic acids. Because vitamin A from animal sources or supplements (e.g., retinol) is preformed, it is more likely to cause toxicity than provitamin A from plant sources (e.g., beta-carotene).

Vitamin A is crucial to cellular differentiation and integrity in the eye, and its deficiency causes xerophthalmia (dryness, fragility and clouding of cornea). It has an important role in phototransduction, and its deficiency causes night blindness, poor bone growth, nonspecific dermatological problems (e.g., hyperkeratosis), and impaired immune function.

Vitamin A deficiency is common among populations in developing countries, and effective replacement approaches were defined for at-risk populations. Additional doses given to individuals with xerophthalmia or children at high risk of vitamin A deficiency, such as those with measles, diarrhea, respiretory disease, or severe malnutrition.

Diagnosis of vitamin A deficiency is usually made by clinical findings, but can be supported by measurement of serum retinol levels, or the ratio of retinol: RBP (a molar ratio <0.8 suggests deficiency).

Recommendations

In persons where dietary intake of vitamin A is adequate, there is no evidence that vitamin A supplementation is helpful for preventing cardiovascular disease, but supplementation may even have harmful effects on cardiovascular mortality, cancer, and bone health.

Acute vitamin A toxicity occurs in adults when a single dose of >660,000 units (>200 mg) of vitamin A is ingested. Chronic toxicity occurs with long-term ingestion of vitamin A doses in amounts higher than 10 times the RDA. Preformed vitamin A can have teratogenic effects during the first trimester of pregnancy, at doses of only several times the RDA.

References

Adcock, IM, Mumby, S, 2017: Glucocorticoids. Handb. Exp. Pharmacol. 237:171

Al Tanoury, Z, Piskunov, A, Rochette-Egly, C, 2013: Vitamin A and retinoid signaling: Genomic & non-genomic effects. J. Lipid Res. 54: 1761-75.

Almohanna**, HM,** Ahmed**, AA,** Tsatalis**, JP,** Tosti**, A, 2019:** The role of vitamins and minerals in hair loss: A review. Dermatol. Ther. (Heidelb). 9, 1:51-70.

Alon, US, 2018: The effects of diuretics on mineral and bone metabolism. Pediatr. Endocrinol. Rev. 15, 4:291-7.

Baytekus, A,Tariku, A, Debie, A, 2019: Clinical vitamin-A deficiency and associated factors in pregnant and lactating women in Northwest

Ethiopia: A community-based cross-sectional study. BMC Pregnancy Childbirth 19, 1:506-11.
Biesalski, HK, 1989: Comparative assessment of the toxicology of vitamin A and retinoids in man. Toxicology 57:117.
Bitot, C, 1863: Gaz. hebd. Mdd. Chir. 10:284.
Bohn, T, Desmarchelier, C, El, SN, Keijer, J, van Schothorst, E, *et al,* 2019: Beta-carotene in the human body: Metabolic bioactivation pathways - from digestion to tissue distribution and excretion. Proc. Nutr. Soc. 78, 1:68-87
Bohn, T, Desmarchelier, C, El, SN, Keijer, J, van Schothorst, E, *et al,* 2019: Beta-carotene in the human body: metabolic bioactivation pathways - from digestion to tissue distribution and excretion. Proc. Nutr. Soc. 78, 1:68-87.
Borowitz, D, Durie, PR, Clarke, LL, *et al,* 2005: Gastrointestinal outcomes and confounders in cystic fibrosis. J. Pediatr. Gastroenterol. Nutr. 41:273-8.
Bronsnick, T, Murzaku, EC, Rao, BK, 2014: Diet in dermatology: Part I. Atopic dermatitis, acne, and nonmelanoma skin cancer. J. Am. Acad. Dermatol. 71, 6:1039e1-12.
Bryer, HP, Isserow, JA, Armstrong, EC, *et al,* 1995: Azathioprine alone is bone sparing and does not alter cyclosporin A-induced osteopenia in the rat. J. Bone Miner Res.10:132-8.
Cañete, A, Cano, E, Muñoz-Chápuli, R, Carmona, R, 2017: Role of vitamin a/retinoic acid in regulation of embryonic and adult hematopoiesis. Nutrients 9, 2:159-62
Cantorna, MT, Nashold, FE, Chun, TY, Hayes, CE, 1996: Vitamin A down-regulation of IFN-gamma synthesis in cloned mouse Th1 lymphocytes depends on the CD28 costimulatory pathway. J. Immunol. 156:2674-9.
C**antorna, MT, Nashold, FE, Hayes, C, 1995:** Vitamin A deficiency results in a priming environment conducive for Th1 cell development. Eur. J. Immunol. 25:1673-8.
Chabra, S, Mayock, DE, Zerzan, J, Bittner, R, Neufeld, MD, *et al,* 2013: Vitamin A status after prophylactic intramuscular vitamin A supplementation in extremely low birth weight infants. Nutr. Clin. Pract. 28, 3:381-6.
Chen, M, Thomson, ABR, Tsin, ATC, Basu, TK, 2003: The hepatic retinyl ester hydrolase activity is depressed at the onset of diabetes in BB rats. Br. J. Nutr. 89, 2:231-8.
Cheruvattath, R, Orrego, M, Gautam, M, *et al,* 2006: Vitamin A toxicity: when one a day doesn't keep the doctor away. Liver Transpl. 12:1888-92.
Chomienne, C, Fenaux, P, Degos, L, 1996: Retinoid differentiation therapy in promyelocytic leukemia. FASEB J. 10:1025.
Conaway, HH, Henning, P, Lerner, UH, 2013: Vitamin a metabolism, action, and role in skeletal homeostasis. Endocr. Rev. 34, 6:766-97.
Crandall, C, 2004: Vitamin A intake and osteoporosis: A clinical review. J. Wom. Hlth. (Larchmt) 13: 939.
Cundy, T, Farquhar, CM, Cornish, J, Reid, I R, 1996: Short-term effects of high dose oral medroxyprogesterone acetate on bone density in premenopausal women. J. Clin. Endocrinol. Metab. 81:1014-8.
Daniels, LA, Davidson, GP, 1989: Current issues in the nutritional management of children with cystic fibrosis. Aust. Pediatr. J. 25, 5:261-6.
Darlow, BA, Graham, PJ, Rojas-Reyes, MX, Cochrane Neonatal Group, 2016: Vitamin A supple- mentation to prevent mortality and short- and long-term morbidity in very low birth weight infants. Cochrane Database Syst. Rev. 8: CD000501.
Dawson**, MI, 2000:** The importance of vitamin A in nutrition. Curr. Pharm. Des. 6, 3:311-25.
de Pee, S, Dary, O, 2002: Biochemical indicators of vitamin A deficiency: serum retinol and serum retinol binding protein. J. Nutr. 132: S2895.
Degos, L, Wang, Z Y, 2001: All trans retinoic acid in acute promyelocytic leukemia. Oncogene 20, 49:7140-5.
El Badri, AM, Salawu, A, Brown, JE, 2019: Bone health in men with prostate cancer: Review article. Curr. Osteoporos Rep. 17, 6:527-37
Feingold, KR, Anawalt, B, Boyce, A, *et al,* 2000: Editors. Endotext [Internet] South Dartmouth (MA): MDText.com, Inc.
Feng, H, Zhang, Z, Qing, X, Wang, X, Liang, C, *et al,* 2016: Promoter methylation of APC & RAR-beta genes as prognostic markers in non-small cell lung cancer (NSCLC). Exp. Mol. Pathol. 100:109-13.
Feranchak, AP, Gralla, J, King R, *et al,* 2005: Comparison of indices of vitamin A status in children with chronic liver disease. Hepatology 42: 782.
Feranchak, AP, Sokol RJ, 2007: Medical and nutritional management of cholestasis in infants and children. In: Liver Disease in Children, 3rd, Suchy FJ, Sokol RJ, Balistreri WF (Eds.), Cambridge University Press, New York.

Feskanich, D, Singh, V, Willett, WC, Colditz, GA, 2002: Vitamin A intake and hip fractures among postmenopausal women. JAMA 287:47.

Freund, C, Gotthardt, DN, 2017: Vitamin A deficiency in chronic cholestatic liver disease: Is vitamin A therapy beneficial? Liver Int. 37, 12:1752-8

Gadhia, MM, Cutter, GR, Abman, SH, Kinsella, JP, 2014: Effects of early inhaled nitric oxide therapy and vitamin A supplementation on the risk for bronchopulmonary dysplasia in premature newborns with respiratory failure. J. Pediatr. 164:744-8.

Geubel, AP, De Galocsy, C, Alves, N, *et al,* 1991: Liver damage caused by therapeutic vitamin A ad-ministration: Estimate of dose-related toxicity in 41 cases. Gastroenterology 100:1701.

Graham-Maar, RC, Schall, JI, Stettler, N, *et al,* 2006: Elevated vitamin A intake and serum retinol in preadolescent children with cystic fibrosis. Am. J. Clin. Nutr. 84:174-7.

Green, AC, Martin, TJ, Purton, LE, 2016: The role of vitamin A and retinoic acid receptor signaling in post-natal maintenance of bone. J. Steroid Biochem. Mol. Biol. 155(Pt A):135-46

Green, MH, Green, JB, Berg, T, *et al*, 1988: Changes in hepatic parenchymal and nonparenchymal cell vitamin A content during vitamin A depletion in the rat. J. Nutr.118:1331.

Guarascio, P, Portmann, B, Visco, G, Williams, R, 1983: Liver damage with reversible portal hypertension from vitamin A intoxication: Demonstration of Ito cells. J. Clin. Pathol. 36: 769-72.

Harrison, EH, 1993: Enzymes catalyzing the hydrolysis of retinyl esters. Biochim. Biophys. Acta 1170:99-102.

Hirsh, J, 1991: Oral anticoagulant drugs. N. Engl. J. Med. 324:1865-8.

Hsiao, C, Clukay, CJ, 2017: Orangeness peeling back the myths behind carotenemia. JAMA Dermatol. 153, 9:873-6.

Huiming, Y, Chaomin, W, Meng, M, 2005: Vitamin A for treating measles in children. Cochrane Database Syst Rev.:CD001479.

Imdad, A, Herzer, K, Mayo-Wilson, E, *et al,* 2010: Vitamin A supplementation for preventing morbidity and mortality in children from 6 months to 5 years of age. Cochrane Database Syst. Rev.:CD008524.

Janczewska, I, Ericzon, BG, Eriksson, LS, 1995: Influence of orthotopic liver transplantation on serum vitamin A levels in patients with chronic liver disease. Scand. J. Gastroenterol. 30:68-72.

Jiang, A, Wang, X, Shan, X, Li, Y, Wang, P, *et al,* 2015: Curcumin reactivates silenced tumor suppressor gene RARbeta by reducing DNA methylation. Phytother. Res. PTR. 29:1237-45.

Johnson, EJ, Russell, RM, 2010: Beta-carotene. In: Coates PM, Betz JM, Blackman MR, *et al*, (eds.) Encyclopedia of Dietary Supplements. 2nd ed. London & New York: Information Healthcare.

Kadri, A, Sjahrir, H, Sembiring, RJ, Ichwan, M, 2020: Combination of vitamin A and D supplementation for ischemic stroke: Effects on interleukin-1ß and clinical outcome. Med. Glas. (Zenica) 17, 2:425-32.

Karrer, P, Morf, R, Schopp, K, 1931: Zur Kenntnis des Vitamins-A aus Fischtranen. Helv. Chim. Acta 14:1036-40.

Katz, J, West, KP Jr, Khatry, SK, *et al*, 1995: Impact of vitamin A supplementation on prevalence and incidence of xerophthalmia in Nepal. Invest. Ophthalmol. Vis. Sci. 36:2577.

Krasinski, SD, Russell, RM, Otradovec, CL, *et al,* 1989: Relationship of vitamin A and vitamin E intake to fasting plasma retinol, retinol-binding protein, retinyl esters, carotene, alpha-tocopherol, and cholesterol among elderly people and young adults: increased plasma retinyl esters among vitamin A-supplement users. Am. J. Clin. Nutr. 49:112-6.

Lam, HS, Chow, CM, Poon, WT, *et al,* 2006: Risk of vitamin A toxicity from candy-like chewable vitamin supplements for children. Pediatrics 118:820.

Lee, TH, 2018: Nutritional assessment and management for patients with chronic liver disease. Korean J. Gastroenterol. 71, 4:185-91.

Leo, MA, Lieber, CS, 1999: Alcohol, vitamin A, and beta-carotene: adverse interactions, including hepatotoxicity and carcinogenicity. Am. J. Clin. Nutr. 69:1071-4.

Li, HX, Zhao, W, Shi, Y, Li, YN, Zhang, LS, *et al,* 2015: Retinoic acid amide inhibits JAK/STAT pathway in lung cancer which leads to apoptosis. Tumor Boil. 36:8671-8.

Lin, P, Fintelmann, RE, Khalifa, YM, *et al,* 2011: Ocular surface disease secondary to vitamin A deficiency in the developed world: it still exists. Arch. Ophthalmol. 129:798-801.

Lopez, AD, Mathers, CD, Ezzati, M, *et al,* 2006: Editors, Global Burden of Disease and Risk Factors, Washington (DC): The International

Bank for Reconstruction & Development/ The World Bank; New York: Oxford University Press.

Mahoney, CP, Margolis, MT, Knauss, TA, Labbe, RF, 1980: Chronic vitamin A intoxication in infants fed chicken liver. Pediatrics 65: 893-8.

Mayo-Wilson, E, Imdad, A, Herzer, K, *et al,* 2011: Vitamin A supplements for preventing mortality, illness, and blindness in children aged under 5: Systematic review and meta-analysis. BMJ 343:d5094.

McLaren, DS, 1981: The luxus vitamins-A and B12. Am. J. Clin. Nutr . 34:1611-6.

Michaëlsson, K, Lithell, H, Vessby, B, Melhus, H, 2003: Serum retinol levels and the risk of fracture. N. Engl. J. Med. 48:287.

Morgan, SL, Weinsier, RL, 1998: Fundamentals of Clinical Nutrition, Mosby, St Louis

Morriss-Kay, GM, Sokolova, N, 1996: Embryonic development and pattern formation. FASEB J. 10:961.

Muir, JM, Andrew, M, Hirsch, J, *et al,* 1996: Histomorphometric analysis of the effects of standard heparin on trabecular bone in vivo. Blood 88:1314-8.

Murzaku, EC, Bronsnick, T, Rao, BK, 2014: Diet in dermatology: Part II- Melanoma, chronic urticaria, and psoriasis. J. Am. Acad. Dermatol. 71, 6:1053e1-16

Myhre, AM, Carlsen, MH, Bøhn, SK, *et al,* 2003: Water-miscible, emulsified, and solid forms of retinol supplements are more toxic than oil based preparations. Am. J. Clin. Nutr. 78:1152-8.

Olson, JA, 1999: Upper limits of vitamin A in infant formulas, with some comments on vitamin K. J. Nutr. 119:1820-5.

Orfanos, CE, Zouboulis, CC, Almond-Roesler, B, Geilen, CC, 1997: Current use and future potential role of retinoids in dermatology. Drugs 53:358.

Penniston, KL, Tanumihardjo, SA, 2006: The acute and chronic toxic effects of vitamin A. Am. J. Clin. Nutr. 83:191-4.

Pfeilschifter, J, Diel, IJ, 2000: Osteoporosis due to cancer treatment: Pathogenesis and management. J. Clin. Oncol. 18:1570-6.

Ratchford, TL, Teckman, JH, Patel, DR, 2018: Gastrointestinal pathophysiology and nutrition in cystic fibrosis. Expert. Rev. Gastro-enterol. Hepatol. 12, 9:853-62.

Rigtrup, KM, Ong, DE, 1992: A retinyl ester hydrolase activity intrinsic to the brush border mem-brane of rat small intestine. Biochemistry 31:2920.

Ross, A, 2006: Vitamin A and Carotenoids. In: Shils M, Shike M, Ross A, Caballero B, Cousins R, eds. Modern Nutrition in Health and Disease. 10th ed. Baltimore, MD: Lippincott Williams & Wilkins.

Ross, AC, 2000: Vitamin A and Retinoids. In: Modern Nutrition in Health and Disease, Shils, M, **Ross, AC, Owusu, SA, 2017**: Vitamin A metabolism. In: the Fetus and Neonatein Fetal and Neonatal Physiology (5th Ed.), eds. Richard A. Polin, Steven H. Abman, ... William W. Fox

Rothman, KJ, Moore, LL, Singer, MR, *et al,* 1995: Teratogenicity of high vitamin A intake. N. Engl. J. Med. 333:1369.

Rougereau, A, Person, O, Rougereau, G, 1987: Fat soluble vitamins and cancer localization associated to an abnormal ketone derivative of D3 vitamin: Carcinomedin. Int. J. Vitam. Nutr. Res. 57, 4:367-73.

Saari, JC, 1994: Retinoids in photosensitive systems. In: The Retinoids: Biology, Chemistry, & Medicine. (Eds.) Sporn, MB, Roberts, AB, Goodman, DS: Raven Press, New York.

Schmitz, J, West, KP, Jr, Khatry, SK, *et al,* 2012: Vitamin A supplementation in preschool children and risk of hearing loss as adolescents and young adults in rural Nepal: Randomised trial cohort follow-up study. BMJ 344:d7962.

Schwartz , E, Zelig, R, Parker, A, Johnson, S, 2017: Vitamin A supplementation for the prevention of bronchopulmonary dysplasia in preterm infants: An update. Nutr. Clin. Pract. 32, 3: 346-53.

Sibulesky, L, Hayes, KC, Pronczuk, A, DiFranco, C, Rosner, B, *et al,* 1999: Safety of < 7500 RE (<25000 IU) vitamin A daily in adults with retinitis pigmentosa. Am. J. Clin. Nutr. 69, 4: 656-63.

Smith, FR, Goodman, DS, 1976: Vitamin A transport in human vitamin A toxicity. N. Engl. J. Med. 294:805.

Sommer, A, West, KP Jr, 1996: Vitamin A deficiency: Health, survival, and vision, Oxford University Press, New York.

Soprano, DR, Soprano, KJ, 1995: Retinoids as teratogens. Ann. Rev. Nutr. 15:111-5.

Stahl, M, Tallman, MS, 2019: Differentiation syndrome in acute promyelocytic leukaemia. Br. J. Haematol. 187, 2:157-62.

Taipale, H, Rysä, J, Hukkanen, J, Koponen,

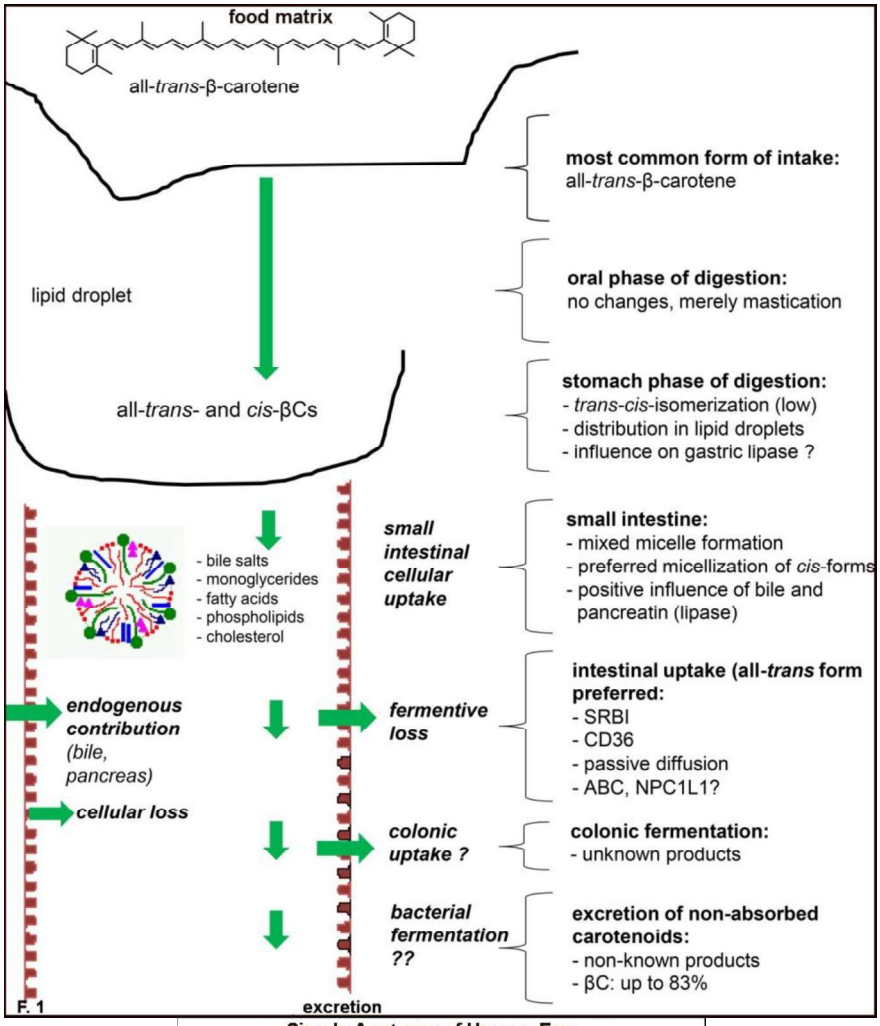
M, Tanskanen, A, *et al,* 2019: Long-term thiazide use and risk of low-engery fractures among persons with Alzheimer's disease-nested case-control study. Osteoporos Int. 30, 7:1481-9.
Underwood, BA, Arthur, P, 1996: The contri bution of vitamin A to public health. FASEB J. 10:1040-6.
Veraldi, S, Pietrobattista, A, Liccardo, D, Basso, MS, Mosca, A, *et al,* 2020: Fat soluble vitamins deficiency in pediatric chronic liver disease: The impact of liver transplantation. Dig. Liver Dis. 52, 3:308-13.
von Hubbenet, M, 1860: Ann. Oculist., Paris, 44:293.
Wald, G, Brown, PK, Smith, PH, 1955: Iodopsin. J. Gen. Physiol. 38, 5:623-81.
Walker, A, Zimmerman, MR, Leakey, RE, 1982: A possible case of hypervitaminosis A in Homo erectus. Nature 296, 5854:248-50.
Wang, J, Dai, Y, Huang, Y, Chen, X, Wang, H, *et al,* 2013: All-trans retinoic acid restores gap junctional intercellular communication between oral cancer cells with upregulation of Cx 32 & Cx43 expressions in vitro. Med. Oral Patholol. Oral Cir. Bucal.18:e569-77.
Weber, FL, Jr, Mitchell, GE, Jr, Powell, DE, *et al*, 1982: Reversible hepatotoxicity associated with hepatic vitamin A accumulation in a protein-deficient patient. Gastroenterology 82: 118.
WHO, 1997: Vitamin A supplements, a guide to their use in treatment and prevention of vitamin A deficiency and xerophthalmia, 2nd Ed, Geneva.
WHO, 2009: Infant and Young Child Feeding: Model Chapter for Textbooks for Medical Students and Allied Health Professionals. Geneva, Switzerland
Williams, GR, Bassett, JHD, 2018: Thyroid diseases and bone health. J. Endocrinol. Invest. 41, 1:99-109.
Williams, SR, 1997: Nutrition and Diet Therapy. 8th Mosby, St Louis.
Wolf, G, 1996: A history of vitamin A and retinoids. FASEB J. 10:1102.
Wolinsky-Friedland, M, 1995: Drug-induced metabolic bone disease. Endocrinol. Metab. Clin. North Am. 24:395-9.

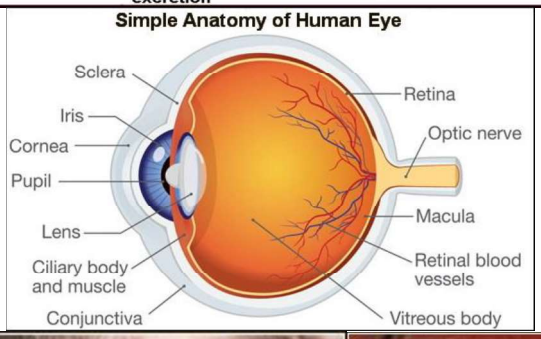
1: Clinical symptoms of selected vitamin deficiencies

Water-soluble	Function	Deficiency syndrome
B1, thiamine	Thiamine pyrophosphate	Beriberi
B2, riboflavin	Flavin adenine dinucleotide	
Niacin, nicotinic acid	Nicotinamide adenine dinucleotide	Pellagra
B6, pyroxidine, pyridoxal	Transaminase cofactor	Anemia
B12, cobalamin	One carbon transfer	Pernicious anemia
Folate	One carbon transfer	Megaloblastic anemia
Biotin	Pyruvate carboxlase cofactor	
Pantothenate	Coenzyme A	
C ascorbate	Antioxidant, collagen synthesis	Scurvy
Fat-soluble	Function	Deficiency syndrome
Vitamin A	Vision, epithelial differentiation	Night blindness, xerophthalmia, keratomalacia, Bitot's spot, follicular hyperkeratosis
Vitamin D	Prohormone for calcium regulation	Rickets, osteomalacia, craniotabes, rachitic rosary
Vitamin E	Antioxidant	Sensory and motor neuropathy, ataxia, retinal degeneration, hemolytic anemia
Vitamin K	Function	Hemorrhagic disease

Table 2: Dietary reference intakes for vitamin A

Vitamin A	Age group	RDA/AI (Mcg daily)	UL (Mcg daily)	Effects of excess
1 mcg retinol activity equivalent = 3.3 unit vitamin A	Infants: 0-6 months	400	600	Ataxia, alopecia, hyperlipidemia, hepatotoxicity, bone and muscle pain; teratogenic
	Infants: 7-12 months	500	600	
	Children: 1 – 3 years	300	600	
	Children: 4 – 8 years	400	900	
	Males: 9- 13 years	600	1700	
	Males: 14 -18 years	600	2800	
	Males: ≥ 19years	900	3000	
	Females: 9- 13 years	600	1700	
	Females: 14 -18 years	700	2800	
	Females: ≥ 19years	700	3000	
	Pregnancy: <18 years	750	2800	
	Pregnancy: > 19 years	770	3000	
	Lactation: <18 years	1200	2800	
	Lactation: 19 years	1300	3000	


food matrix
all-trans-β-carotene
most common form of intake:
all-trans-β-carotene
lipid droplet
oral phase of digestion:
no changes, merely mastication
all-trans- and cis-βCs
stomach phase of digestion:
- trans-cis-isomerization (low)
- distribution in lipid droplets
- influence on gastric lipase ?
- bile salts
- monoglycerides
- fatty acids
- phospholipids
- cholesterol
small intestinal cellular uptake
small intestine:
- mixed micelle formation
- preferred micellization of cis-forms
- positive influence of bile and pancreatin (lipase)
endogenous contribution (bile, pancreas)
fermentive loss
intestinal uptake (all-trans form preferred:
- SRBI
- CD36
- passive diffusion
- ABC, NPC1L1?
cellular loss
colonic uptake ?
colonic fermentation:
- unknown products
bacterial fermentation ??
excretion of non-absorbed carotenoids:
- non-known products
- βC: up to 83%
F. 1
excretion


Simple Anatomy of Human Eye
Sclera
Iris
Cornea
Pupil
Lens
Ciliary body and muscle
Conjunctiva
Retina
Optic nerve
Macula
Retinal blood vessels
Vitreous body


Vitamins esential for elder's eyes
Vitamin A --- Xerophthalmia