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HEPATIC UPTAKE, STORAGE AND RELEASE OF VITAMIN A IN HUMANS

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ABSTRACT

Vitamin A is an essential lipophilic biomolecule for many vital metabolic functions such as vision, placental and embryonic development, reproduction, growth, and has a regulatory role in the immune system. Vitamin A cannot be synthesized in the body, so its prime source is dietary products. Moreover, it has a confirmed role as an antioxidant against oxidative stress due to the excessive presence of free radicals as a result of multiple metabolic processes. However, hypervitaminosis A and toxicity may occur as a consequence of ingesting large amounts of vitamin A. So, proper intake of vitamin A, absorption, metabolismin the liver, storage and then targeting the peripheral tissues are all crucial for the proper functioning of the human system.The present review paper is carried out to explain the different aspects which are related to vitamin A metabolism, storage, and release.

Keywords: Vitamin A, Retinol binding proteins, Retinoid, Chylomicrons, Hepatic stellate cells

1. INTRODUCTION

Vitamin A is a fat-soluble, essential nutrient with a pivotal role in various metabolic and physiological processes within the body **[1]**. Structurally, vitamin A belongs to a group of unsaturated compounds that includes retinol, retinal, retinoic acid, and several provitamin A carotenoids.

Vitamin A is found in plant and animal products in the form of provitamin A carotenoids and retinoids, respectively **[2]**. Retinoids are compounds that consist of four isoprenoid unitscontaining five carbon-carbon double bonds and a functional terminal group. Although retinoids in animals are present in different forms, analogs that were chemically synthesized may or may not have specific biological activity **(Figure 1)**.

The major sources of vitamin A among the plants are green vegetables, yellow vegetables, vegetable oils, and yellow fruits. Whereas, in animal products, liver, fish oil, milk, eggs, and dietary products are rich in vitamin A. The recommended dietary allowance (RDA) values of vitamin A for different ages and genders are mentioned in **Table 1 [3]**.

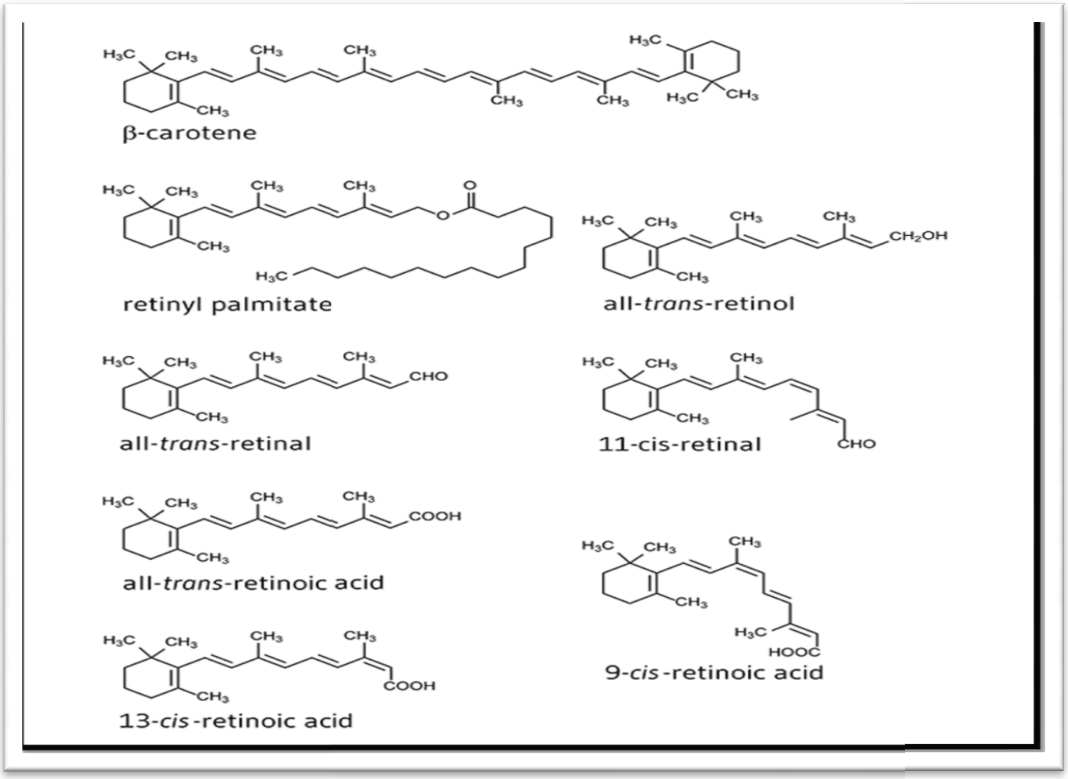

Figure 1: The structures of the major dietary forms of vitamin A (adopted from [4])

Table 1: RDA for vitamin A according to age and gender

	Retinol Activity Equivalent (RAE in µg)			
Age (years)	**Male**	**Female**	**Pregnancy**	**Lactation**
≤0.5*	**400**		**-**	**-**
≥ 0.5*	**500**		**-**	**-**
1–3	**300**		**-**	**-**
4–8	**400**		**-**	**-**
9–13	**600**		**-**	**-**
14–18	**900**	**700**	**750**	**1,200**
19–50	**900**	**700**	**770**	**1,300**
≥ 51	**900**	**700**	**-**	**-**
*** Equivalent to breast fed infants**				

In the human body, retinol is used in the form of retinal that is oxidized into retinoic acid; while provitamin A compounds of plant source like β-carotene converted into the form of retinol to be used by the human body. β-carotene is classified as a provitamin A carotenoid and is uniquely synthesized by plants. On the contrary, retinyl esters are vitamin A compounds that are found in the fat-soluble molecules of animal products. Retinyl esters are consumed by the human body in the form of trans-retinols that are spontaneously hydrolyzed from retinyl esters in the liver. As a result, trans-retinols will bind to retinol-binding proteins (RBPs) to form retinol-binding protein- trans retinol complexes that are readily transported into the bloodstream **[5]**. As for vitamin A storage, it is stored in the liver until it is required for consumption, whereas vitamin A retinols and the other provitamin A carotenoids are also stored in the upper gastrointestinal tract **[6]**.

Vitamin A helps in carrying out functionaries that are directly or indirectly related to tissues homeostasis, metabolism of lipids, and differentiation of cells. Besides, vitamin A compounds are also responsible for performing cell differentiation process and gene expression for carrying out treatments. As a result, due to the high medicinal qualities of vitamin A; it is used by multiple pharmaceutical companies in order to make therapeutic doses for the treatment of chronic diseases like HIV and cancer **[7]**. Furthermore, Vitamin A is highly beneficial for developing the immune system by providing a protective shield to the body. It regulates the functioning of different cells and genes like T lymphocytes that helps in protecting the body from different abnormal reactions **[8]**.

Vitamin A is also used for the treatment of hair fall, acne, photoaging, and psoriasis. It is also considered as an essential compound that protects the vision and provides strengths to the eyes. For example, retinal (a vitamin A preformed compound) directly combines with opsin,

(an eye protein that presents in retina) and results in the formation of a compound termed as rhodopsin which helps to protect the eyes from different infections and adapting human vision at the time of dark light. Vitamin A is also responsible for reducing the risk of cancer by regulation of cell proliferation. Vitamin A can promote several biological activities such as antioxidant functionality, healthy growth of bones and body, protection against age-related macular degeneration, synergistic effect on vitamin D, and others **[9]**.

Vitamin A deficiency mainly occurs due to chronic insufficient intake of vitamin A

while it could be reversed by consuming animal or plant vitamin A -containing products. Vitamin A deficiency results in numerous disorders among the children, women who belong to reproductive age, and the individuals who are suffering from poor absorption levels of lipids. The presence of inflammatory bowel diseases affects the consumption and utilization of vitamin A strongly, which results in the incidence of chronic diseases like Crohn's disease and celiac disease **[10]**.

It has been estimated that when serum retinol is lower than 0.70 μM (or <20 μg/dL), it is considered as vitamin A deficiency. However, if the levels of serum retinol fall and reach the serious depletion of vitamin A in the body; numerous pathological complications are predicted, like blindness, infectious diseases, thyroid dysfunction, and other disorders **[11]**. Vitamin A deficiency results in superficial buildup of different shapes of keratin on the conjunctiva of the eye, Bitot's spots, and night vision abnormalities. Furthermore, vitamin A deficiency may result in the incidence of immunodeficiency diseases, respiratory complications, and low synthesis of thyroid-stimulating hormone (TSH). Hence, vitamin A intake is good for health and therefore the right amount of vitamin A is recommended for maintaining good health for individuals **[12]**.

2. FATE OF DIETARY VITAMIN A

2.1 Absorption

2.1.1 Provitamin A carotenoids

Following carotenoids ingestion and digestion, carotenoids are passively diffused in the small intestine cells (enterocytes). However, the percent of absorption may decrease with high intake. In the small intestine, β-carotenes are converted to retinoids via two cleavage reactions. The first reaction is mediated by the enzyme β-carotene-15-monooxygenase at the 15,15-carbon double bond. This cleavage yields two compounds of retinal. The second reaction is termed as an asymmetric eccentric cleavage and results in the formation of two different chain lengths of β -apo carotenals **[7]**. The longer chain, however, is shortened by β, β carotene 9,10-dioxygenase enzyme to retinoic acid or retinal. Furthermore, intestinal-produced retinal is subsequently reduced to retinol **[13]**.

2.1.2 Retinol and retinyl esters

Before absorption takes place and in the small intestine, dietary retinyl esters are hydrolyzed by pancreatic enzymes, lipase, and phospholipase B, to retinol. After hydrolysis, enterocytes engulfretinol via a protein carrier-mediated process.Besides, a diffusion-dependent process may also be engaged in retinol, and retinyl esters

transport through enterocytes membrane **[14]**.

2.2 Secretion by intestinal cells

In enterocytes, retinol is re-esterified with long-chain fatty acids. This process starts with retinol binds to cellular binding protein type II (CRBP-II). The latter protein is expressed in the intestinal mucosa. Such binding facilitates retinol esterification by the enzyme lecithin: retinol acyltransferase (LRAT), and to protect retinol from enzymatic degradation **[15]**.

The majority of the formed retinyl esters are then incorporated into the fat, triglycerides and phospholipids, of chylomicrons, an intestinal synthesized lipoprotein. These large lipoprotein complexes are secreted from the enterocytes into the intestinal lymph, while a significant amount of unesterified retinol is also secreted into the portal circulation **[16]**.

3. LIVER METABOLISM OF VITAMIN A AND STORAGE

3.1 Vitamin A metabolism

After the release into the lymphatic system, chylomicrons enter the circulation through the thoracic duct and then undergo lipolysis via lipase enzyme and apolipoprotein exchange with extrahepatic tissues. The latter lipolysis leads to decrease in chylomicron size to become remnants of chylomicron remnants. The retinyl esters that were held by chylomicrons will remain within its remnants. The chylomicron remnants are mainly taken up by liver parenchymal cells (hepatic uptake) via LDL receptors. Furthermore, extrahepatic uptake of chylomicron remnants occurs in bone marrow, adipose tissue, skeletal muscles, kidneys, spleen, and peripheral blood cells **[17]**.

In hepatocytes, the hydrolysis of retinyl esters into retinol occurs concurrently with the association of unesterified retinol to retinol-binding proteins (RBPs). RBP is a protein that is found intensively in hepatocyte endoplasmic reticulum, binding of retinol to RBPs will initiate the translocation of retinol-RBP complex from the endoplasmic reticulum to the Golgi complex, which will be followed by direct secretion of these complexes into plasma. In addition, a large portion of retinol is transferred to a perisinusoidal stellate cell for storage as retinyl esters **[18]**.

3.2 Vitamin A storage in the liver

In healthy individuals, up to 80% of human body's retinol is stored in the liver, and 70-90% of it is stored in the hepatic perisinusoidal stellate cells. The cytoplasm of stellate cells contain high levels of aggregatesof lipid droplets containing retinyl esters. Furthermore, it has been found that that a CRBP-I, which has high

homology with CRBP-II, and LRAT are highly expressed in hepatic stellate cells and critical enzymes for the storage of retinyl esters.

In healthy individuals, the storage of retinyl esters in stellate cells should be an adequate supply of vitamin A for several weeks or months. Such storage controls the conversion of retinyl esters to retinol and the mobilization of retinol to circulation. This regulatory mechanism of release of retinol to blood ensures an almost constant blood plasma retinol concentration of ~2 μM **[19]**.

3.3 Vitamin A Storage in extrahepatic tissues

After ingesting large amounts of vitamin A, accumulation in the small intestine as well as extrahepatic organs do occur of lipid droplets containing retinyl esters. This extrahepatic storageis believed essential to local tissue supply of vitamin A. For instance, the storage of retinyl ester in retinal pigment epithelial cells is necessary for normal visual function. In the eyes, the photoreceptors of retina are very well enriched with retinaldehyde (retinal). In contrast, the retina and retinal pigmented epithelium (RPE) contain high concentrations of both the 11-cis- and all-trans-isomers of retinaldehyde, retinol, and retinyl ester. Furthermore, these RPE cells express high levels of LRAT and possess retinyl ester hydrolase (REH) enzymatic activity **[20]**.

Adipose tissue, on the other hand, stores 0.60 - 0.85 μg of retinol and retinyl esters/106 adipocytes, which accounts for ~10–20% of the total retinoid in the body. Furthermore, RBP is synthesized and secreted from adipose tissue **[21]**. Under conditions of dietary vitamin A deficiency and decreasing circulatory of retinyl esters, adipose retinol/retinyl ester stores are readily mobilized into circulation **[22]**.

4. TRANSPORT IN PLASMAOF RETINOIDS AND CAROTENOIDS

4.1 Retinol transport in plasma

In plasma, retinol-binding proteins (RBPs) act as an essential vehicle for carrying out retinol transport mechanisms. RBPs consist of a specialized hydrophobic pocket that binds and protects the fat-soluble molecule retinol. In addition, RBPs play a vital role in the performing functionaries related to gene expression modulation overall growth and development of the embryo **[23]**.

As mentioned above, the plasma concentration of retinol-RBP is regulated and controlled at 1-2 μM/ml despite the daily intake of vitamin A. Furthermore, approximately95% of the plasma retinol-RBP complex in the circulation binds another plasma protein, transthyretin (TTR) (1:1). This binding stabilizes the retinol-RBP complexand reduces the glomerular

filtration of retinol **[24]**. In severe vitamin A deficiency, retinyl esters in the liver are depleted, and therefore, the concentration of plasma retinol-RBP is decreased.

On the cells, cellular retinoic acid-binding proteins (CRABPs) are the receptors for binding to retinoic acid and induce their biological function through signaling pathways **[25]**. CRABPs, include CRBP I/II, are mainly associated with transporting and metabolites of vitamin A. As a result, there is a conversion of retinol into retinyl esters or retinoic acid so that they could be appropriately stored.

4.2 Other retinoids transport in plasma

Several other forms of retinoidsinclude all-trans retinoic acid, 13-cis retinoic acid, 13-cis-4-oxo retinoic acid, all-trans-4-oxo retinoic acid, and all-trans retinyl β glucuronide are presented in plasma in<10nM. Except for all-trans-retinyl β-glucuronide, these retinoids are transported in plasma by binding to albumin. Furthermore, it has been found in vitro that these retinoids are biologically active **[26]**.

4.3 Carotenoidstransport in plasma

As mentioned earlier, following carotenoids ingestion, they are bound to chylomicrons in the intestine cells and enter the lymphatic system. Thus, carotenoids are transported in plasma by lipoproteins. In the liver, carotenoids do not accumulate in hepatocytes, but are mobilized in conjunction of very low density lipoprotein (VLDL) particles. Furthermore, carotenoids stay bound to VLDL even when VLDL undergoes metabolic reactions to become VLDL remnants and then to low-density lipoprotein (LDL) **[27]**.

5. CELLULAR FORMATION OF RETINAL AND RETINOIC ACID

After absorption, retinyl esters-chylomicrons complexes are secreted to circulation. Following the lipolysis of chylomicrons, chylomicron remnants bound to retinyl esters are taken up by hepatocytes via LDL receptors. Inside the hepatocytes, the retinyl esters are hydrolyzed by retinyl ester hydrolase enzyme to form retinol. Retinol has two fates; it can be either complexed with RBP and transthyretin released into the plasma or re-esterified by LRAT and DGAT1 in the hepatic Stellate cells for long-term storage **[28]**.

The retinol circulates in plasma as RBP and transthyretin and retinol complex. To enter the target cells in the peripheral tissues, the latter complex binds to “stimulated by retinoic acid gene 6 homolog” (STRA6), which facilitates the complex uptake **[29]**. Inside the target cells, the retinol is oxidized to retinal and then to retinoic acid **[30]**. This reaction forms all active retinoid metabolites, such as all-trans retinoic acid (atRA), 9-cis retinoic acid (9cRA), and 9-

cis-13,14 dihydroretinoic acid (9cDHRA) **[31]**.

6. ASSESSMENT OF VITAMIN A STATUS

Although historically assessment of vitamin A deficiency was by looking for signs and symptoms of xerophthalmia and night blindness, it is still used in undeveloped areas of the world. Currently, however, clinical methodologies to assess the status of vitamin A in the human body are by measuring retinol and RPB in serum or plasma. Although measuring serum retinol is a standard and gold method, it is homeostatically controlled to be around 2 μM until liver reserves become dangerously low. Therefore, it is assumed that measuring retinol is a surrogate biochemical indicator of vitamin A stores in the liver only when liver storage of vitamin A exists regardless of the amount stored **[32]**. Furthermore, the method of analysis of retinol is done only in reference laboratories and would be difficult to use in the general population, especially in undeveloped and rural areas.

Since RBP binds to retinol in the liver in approximately 1:1 ratio before it complexes with transthyretin and then secreted to the circulation, measuring RBP would be an indicator of retinol in serum and thus will be a surrogate biomarker of vitamin A status. Furthermore, measuring RBP can be performed in small laboratories and can be used to assess populations in undeveloped and rural areas. In certain conditions such as low glomerular function rate or zinc deficiency, however, measuring RBP in patients with, it would result in a false result **[33]**.

Even in vitamin A adequate populations, it has been found that serum retinol and RBP levels are lower in infants and young children than in adults. Therefore, the reference ranges should be varied to age. Furthermore, RBP concentrations do not vary by gender. In contrast, serum retinol concentrations in middle-age women is lower than in men counterpart. The latter could be associatedwith the higher prevalence of inflammation in women or the difference in liver storage between genders **[33]**.

7. VITAMIN A EFFICIENCY FOR VISION

The retina consists of two major types of receptors; it includes light-sensitive receptor cells and the cone photoreceptor cells. Both parts help in the proper functioning of the retina and are mainly used to convert the light rays into electric signals. Retina also includes the trans-retinol that is transmitted with the help of retina and helps in the accumulation and circulation of retinal pigment epithelial cells. Trans retinol is a precursor to the

formation of the photopigment rhodopsin. To form rhodopsin, trans retinol is converted by isomerase enzyme to 11-cis-retinol and then to 11-cis-retinal **[34]**. Another pathway is by conversion of all-trans-retinol to all-trans-retinal and then to 11-cis-retinal. The resulted 11-cis-retinal can combine with scotopsin to form the rhodopsin.

Rhodopsin plays a crucial role in night vision. When rhodopsin absorbs light in the rods, it yields to a conformational change of 11-cis-retinal to become all-trans-retinal. Also, rhodopsin undergoes several metabolic modifications to the active form, metarhodopsin II. On the rod cell, the metarhodopsin II binds and stimulates transducin, a G-coupled protein found on the outer membrane surface of the cell, which activates cGMP phosphodiesterase. This activation will remove the cGMP mediated activation of cGMP-gated channels that permits Na+ ions to pass into the rod cytoplasm, resulting in rod cell hyperpolarization. Thus, in the presence of light, the process allows the messages about seen the light during night vision to be sent to the brain for final interpretation **[35]**.

8. HEALTH RISKS OF EXCESSICE VITAMIN A

Since vitamin A is fat-soluble, it can be stored in the body in an accumulative pattern leading to hypervitaminosis A. The signs and symptoms of hypervitaminosis A depend on the body size and speed of the excessive dietary intake by either natural or synthetic supplements of retinoids. Chronic intake of excess vitamin A leads to skin irritation, dizziness, nausea, pain in joints and bones, headache, elevated intracranial pressure, coma, and even death. Furthermore, following high consumption of vitamin A, it takes long time for high levels to be cleared from the body, and this may result in irreversible liver damage **[36]**.

In children, a high intake of preformed vitamin A (> 1,500 µg daily; slightly higher than the RDA), was correlated with a reduced bone mineral density that may lead to increased fracture risk **[36]**. In pregnancy, if the oral intake of preformed vitamin A exceeds the 2000 µg, it can cause congenital birth defects. Thus, pregnant women mustn't take high doses of vitamin A supplements. On the other hand, excessive intake of beta-carotene, or carotenoids, is not known to be teratogenic or lead to reproductive toxicity. However, it is associated with harmless discoloration of the skin called carotenemia that can be reversed by discontinuing beta-carotene ingestion **[37]**.

Table 2: Tolerable upper intake levels for preformed vitamin A [38]

	Retinol Activity Equivalent (RAE in µg)		
Age (years)	**Male or Female**	**Pregnancy**	**Lactation**
<1	**600**	**-**	**-**
1–3	**600**	**-**	**-**
4–8	**900**	**-**	**-**
9–13	**1,700**	**-**	**-**
14–18	**2,800**	**2,800**	**2,800**
≥ 19	**3,000**	**3,000**	**3,000**

CONCLUSION

Vitamin A is an essential lipophilic biomolecule for many vital metabolic functions such as vision, placental and embryonic development, reproduction, growth, and has a regulatory role in the immune system. It exists in three major forms: aldehyde isoform named retinal, alcohol isoform named retinol, and retinoic acid, which is the irreversibly oxidized form of retinol. Vitamin A deficiency leads to several serious diseases. The present review paper is showed the aspects of vitamin A metabolism, storage, and release. The study helps providing adequate information about the mobilization and transport of vitamin A metabolites and sites of synthesis and is useful to other scholars and researchers for carrying out their research in the same field.

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