Role of vitamin A in child health and nutrition

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\textbf{ABSTRACT}

Vitamin A is a fat-soluble vitamin. It is essential for vision, especially dark adaptation, immunity, bone growth and reproduction, maintain surface of cornea and sclera, and epithelial integrity of respiratory, urinary and gastro intestinal tract. Vitamin A also has a role in gene expression. Recommended daily allowance for children ranges from 400 to 700 μg. Normal plasma retinol levels are 20–50 μg/dL. Deficiency results in problems in the eye and vision, cellular differentiation, and functionality of the humoral and cell mediated immune system. World Health Organization recommends supplementation approaches in children between 6 and 59 months of age in certain populations at risk of deficiency.

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Vitamin A consists of lipid-soluble compounds called retinoic acids (RA). RA consists of four isoprenoid units joined in a linear fashion. Vitamin A was the first fat soluble vitamin to be discovered in 1913.\textsuperscript{1} Ancient Egyptians, however, had recognized that night blindness could be treated by consumption of liver. Other fat-soluble vitamins are vitamin D, K and E. Vitamin A is essential for vision, especially dark adaptation, immunity, bone growth and reproduction, maintain surface of cornea and sclera, and epithelial integrity of respiratory, urinary and gastro intestinal tract.\textsuperscript{2} Vitamin A also has a role in gene expression.

Vitamin A deficiency (VAD) is widely prevalent globally with almost one-third of children under five years of age living in low and middle income countries being affected. Prevalence is almost 44% in South Asia and 48% in Sub-Saharan Africa. Up to 95% of VAD related deaths due to measles and diarrhea occur in these two regions.\textsuperscript{5} VAD is as a result of poor intake of vitamin A rich food and inadequate dietary diversification. However, in the last two decades there has been a global reduction in VAD from 39% to 33% in children.\textsuperscript{2}

\section*{1. Sources}

Vitamin A from diet is available as either as preformed vitamin A, mainly as retinyl esters such as retinyl palmitate or as provitamin (carotenoids), such as β carotene, α carotene and β cryptoxanthene. Preformed vitamin A in primarily found in foods from animal origin, highest being in organ meats (liver, kidney) and to lesser extent in other meats and milk and milk products (Table 1).\textsuperscript{3} Provitamin A is mainly found in yellow orange fruits and vegetables and in green leafy vegetables, but has lower bioavailability (20–30%). Vitamin A is synonymous with retinol.\textsuperscript{4,5}

Within the body all precursors are converted into two essential active metabolites of Vitamin A, all trans retinoic acid and 11-cis retinol. Cellular differentiation and gene transcription is regulated by all-trans retinoic acid whereas visual pigments rhodopsin and iodopsin require 11-cis retinol.\textsuperscript{4,5}

\section*{2. Metabolism}

This depends upon the type of Vitamin A ingested (See Fig. 1). Metabolism of provitamin A into an active form is regulated by negative feedback mechanism, hence toxicity after excessive intake does not occur.\textsuperscript{3} After consumption, preformed Vitamin A, β carotene and carotenoids, are converted to retinol in human body by small intestines by first splitting it into retinal which is then reduced to retinol. On the other hand, preformed vitamin A metabolism is efficient but not regulated; hence excessive intake can result in toxicity. Hydrolysis of preformed vitamin A into retinol occurs in the lumen of small intestine by various retinyl ester hydrolases found in the brush border of intestinal mucosa. Once absorbed, retinol is re-esterified into retinyl-esters and excreted into blood after incorporation into chylomicrons. In the blood, chylomicrons are broken down to apolipoproteins containing retinol esters. Hepatocytes take up apolipoproteins and combining them with retinol binding protein (RBP) for storage in hepatic stellate cells. Liver stores 50–85% of body’s retinol.\textsuperscript{4} Retinol-RBP complex are released in the plasma to reach the target organs.

Normal plasma retinol levels are 20–50 microgm/dL in infants and increase gradually during childhood. Retinol levels are lower in
Table 1
Vitamin A rich animal and plant sources of food [Adapted from 6].

<table>
<thead>
<tr>
<th>Vegetables</th>
<th>Serving Size</th>
<th>Vitamin A (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweet potato, with skin, cooked</td>
<td>1 medium (114 g)</td>
<td>1096 (mcg)</td>
</tr>
<tr>
<td>Pumpkin, canned</td>
<td>125 mL (½ cup)</td>
<td>1007 (mcg)</td>
</tr>
<tr>
<td>Carrots, cooked</td>
<td>125 mL (½ cup)</td>
<td>653-709 (mcg)</td>
</tr>
<tr>
<td>Carrot, raw</td>
<td>1 medium (61 g)</td>
<td>509 (mcg)</td>
</tr>
<tr>
<td>Kale, fresh or frozen, cooked</td>
<td>125 mL (½ cup)</td>
<td>468-505 (mcg)</td>
</tr>
<tr>
<td>Spinach, cooked</td>
<td>125 mL (½ cup)</td>
<td>498 (mcg)</td>
</tr>
<tr>
<td>Lettuce, romaine</td>
<td>250 mL (1 cup)</td>
<td>258 (mcg)</td>
</tr>
<tr>
<td>Lettuce, red leaf</td>
<td>250 mL (1 cup)</td>
<td>218 (mcg)</td>
</tr>
<tr>
<td>Bok choy, cooked</td>
<td>125 mL (½ cup)</td>
<td>190 (mcg)</td>
</tr>
<tr>
<td>Rapini, cooked</td>
<td>125 mL (½ cup)</td>
<td>150 (mcg)</td>
</tr>
<tr>
<td>Red peppers, cooked</td>
<td>125 mL (½ cup)</td>
<td>106 (mcg)</td>
</tr>
<tr>
<td>Fruits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apricots, dried</td>
<td>60 mL (¼ cup)</td>
<td>191 (mcg)</td>
</tr>
<tr>
<td>Mango</td>
<td>1 large (80 g)</td>
<td>172 (mcg)</td>
</tr>
<tr>
<td>Watermelon</td>
<td>1 wedge (25 g)</td>
<td>80 (mcg)</td>
</tr>
<tr>
<td>Papaya</td>
<td>1 small (25 g)</td>
<td>74 (mcg)</td>
</tr>
<tr>
<td>Guava</td>
<td>1 medium (50 g)</td>
<td>17 (mcg)</td>
</tr>
<tr>
<td>Pink or red grapefruit</td>
<td>100 g</td>
<td>58 (mcg)</td>
</tr>
<tr>
<td>Animal Sources</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>1 tsp (5 ml)</td>
<td>1350 (mcg)</td>
</tr>
<tr>
<td>Liver sausage</td>
<td>1 slice (15 g)</td>
<td>1495 (mcg)</td>
</tr>
<tr>
<td>Lamb liver</td>
<td>1 ounce (25 g)</td>
<td>6421 (mcg)</td>
</tr>
<tr>
<td>Liver, turkey, cooked</td>
<td>75 g (2 ½ oz)</td>
<td>16950 (mcg)</td>
</tr>
<tr>
<td>Liver, veal, cooked</td>
<td>75 g (2 ½ oz)</td>
<td>15052-15859 (mcg)</td>
</tr>
<tr>
<td>Milk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cow</td>
<td>100 ml</td>
<td>52.72 μg</td>
</tr>
<tr>
<td>Buffalo</td>
<td>100 ml</td>
<td>48.48 μg</td>
</tr>
<tr>
<td>Human (Breast Milk)</td>
<td>100 ml</td>
<td>64.24 μg</td>
</tr>
<tr>
<td>Skim, 1%, 2%, chocolate milk</td>
<td>250 mL (1 cup)</td>
<td>137-163 (mcg)</td>
</tr>
<tr>
<td>Curd (Cow's Milk)</td>
<td>100 g m</td>
<td>30.90 μg</td>
</tr>
<tr>
<td>Cheese</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheese</td>
<td>100 g m</td>
<td>82.72 μg</td>
</tr>
<tr>
<td>Cottage Cheese</td>
<td>100 g m</td>
<td>110.90 μg</td>
</tr>
</tbody>
</table>

Children from India and other developing countries due to low intake of preformed vitamin A. Low birth weight and preterm infants also have lower vitamin A hepatic stores. Vitamin A deficiency is seen in malnourished children due to impaired synthesis of RBP. Reduced synthesis of RBP and transthyretin (TTR) are also seen in inflammatory conditions and hence retinol levels are low in such states.

3. Dietary requirements

For healthy population recommended daily allowances (RDA) of vitamin A is expressed as retinol activity equivalent (RAE). For conversion 1 RAE = 1 mcg of all-trans retinol = 12 μg or β carotene, 24 μg α carotene or β cryptoxanthin. One RAE = 1 mcg retinol or 3.3 I.U. Dietary requirements in different age-groups is given in Table 2.

4. Actions

Vitamin A has role in growth, vision, epithelial differentiation, immune function and reproduction. Major biological actions of Vitamin A are in vision, cellular differentiation and immunity.

a) Vision: Vitamin A prevents xerophthalmia, or dryness of corneal and conjunctival, and phototransduction. Retina has two photoreceptors, cones and rods. Cone cells, with iodopsin, are responsible for color vision and rod cells, with rhodopsin, for night-vision. Visual pigments, rhodopsin and iodopsin, are formed by conversion of all-trans-retinol to 11-cis-retinol followed by combination with a membrane-bound protein.

b) Cellular differentiation: To maintain integrity in the eye, respiratory and genito-urinary epithelium and skin.

c) Functionality of the humoral and cell mediated immune system: Through direct and indirect effects on the phagocytes and T cells.

5. Clinical manifestations of vitamin A deficiency (VAD)

Functional indicators of VAD are clinical ophtalmic signs of VAD. Eye signs develop insidiously and are usually seen after 2 years of age. These are graded by WHO as follows:

1. Night blindness (nyctalopia) (XN)
2. Conjunctival xerosis (XIA)
3. Bitot’s spots (XIB)
4. Corneal Xerosis (X2)
5. Corneal ulcer covering less than 1/3 of the cornea (X3A)
6. Corneal ulcer covering at least 1/3 of cornea, defined as Keratomalacia (XS)
7. Xerophthalmia fundus (XF)

Night blindness due to VAD is reversible. VAD results in hyperkeratosis with proliferation of basal cells and formation of stratified cornified squamous epithelium. These changes manifest as growth impairment including poor bone growth, increased susceptibility to respiratory and urinary tract infection and skin changes over arms, legs, shoulders and buttocks. Skin become dry and scaly and this is known as phrynoderma. Protein energy malnutrition results in impaired synthesis of RBP, resulting in Vitamin A deficiency. Concomitant zinc deficiency increases the risk of vitamin A deficiency.

6. Measurement of vitamin A levels

Gold standard for Vitamin A status is its hepatic content, which is difficult to measure. Other quantitative surrogate biochemical indicators are serum retinol concentrations and serum or blood RBP, both of which are highly correlated. Serum retinol reflects liver stores when they are either severely depleted (< 0.07 μmol/L) or extremely high (> 1.05 μmol/L). Between these two extremes, retinol levels, which are under homeostatic control, do not reflect liver Vitamin A reserves.

Serum retinol estimations: This is done by High Performance Liquid Chromatography, an expensive technique, which also may give unreliable results when levels are low. RBP estimations are done by rapid enzyme based immunooassay or radial immunodiffusion technique, both of which are not expensive. Therefore, for population based assessment of VAD RBP protein can be estimated along with biomarkers of inflammation like serum ferritin, transferrin or C-reactive protein levels. RBP is a negative acute phase reactant since its production by the liver increases the risk of vitamin A deficiency.

Other quantitative estimation techniques: For estimation of Vitamin A levels, other quantitative techniques have also been developed such as dose response test and isotope dilution techniques but these are used in experimental conditions. These can be used when hepatic vitamin A reserves are likely to be low. As hepatic vitamin A reserves become depleted apo-RBP accumulates in the liver. When a vitamin A challenge
dose is given, it binds to this accumulated protein and serum RBP concentrations increase within few hours. This forms the basis of dose response test. In this test RBP levels have to be estimated twice, once at baseline and second time after 5 h. In several countries, modified relative dose response test has been used to estimate deficiency wherein RBP estimation is done only once after challenge with a measurable isomer of retinol.15 Isotope dilution assays are also available that trace total body vitamin A reserves.15

7. Treatment of VAD

Children with sub-clinical VAD should be given 1500 μg of vitamin A followed by RDA. In children with clinical signs of VAD 30–60 mg (100,000–200,000 i.u) of vitamin A, according to age categories, are to be given once or twice.14

- Infants < 6 months of age: 50,000 international units orally
- Infants 6–12 months of age: 100,000 international units orally
- Children > 12 months: 200,000 international units orally

In children with xerophthalmia, the above doses are given on day one, day two and day fourteen.

8. Prevention of VAD

World Health Organization (WHO) recommends supplementation approaches in children between 6 and 59 months of age14 in populations with 1% or higher prevalence of night blindness in children 24–59 months of age or where 20% or more children between 6 and 59 months of age have serum retinol level 0.7 μmol/l or below. Same guidelines are there for HIV positive children.16 Supplementation guidelines are as below:

- Infants 6–12 months of age: 100,000 international units orally (30 mg retinol equivalent) as retinyl palmitate or retinyl acetate–One dose
- Children 12–59 months of age: 200,000 international units orally (60 mg retinol equivalent) as retinyl palmitate or retinyl acetate–four to six monthly.

Other strategies for prevention of VAD are through dietary modifications to promote consumption of Vitamin A and β-carotene rich food through education and ensuring their availability locally by modifications in horticultural practices.2 Also fortification of widely consumed food has also been in practice.

Pregnant women living in areas of endemic vitamin A deficiency should receive vitamin A supplementation to prevent night blindness. It is recommended that they get frequent small doses not exceeding 10,000 international units daily or 25,000 international units, given weekly for a minimum of 12 weeks during pregnancy until delivery.17 High-dose supplements is teratogenic and must not be given to pregnant women.

9. Targeted supplementation of vitamin A

This is recommended by WHO for children living in areas of endemic VAD who develop diseases which can further accentuate this deficiency such as measles, diarrhea, respiratory disease, or severe malnutrition. WHO recommended dosage schedule for those who have not received vitamin A in the previous four months is the same as for those with clinical signs of VAD and has been given above. High-risk measles case are to receive the same dose on two successive days,18 and a third dose two to four weeks later if there are ocular manifestations of vitamin A deficiency.

10. Hypervitaminosis A

Excessive intake of vitamin A, usually more than 10 RDA, as pre-formed or food supplements for several weeks, can result in chronic Vitamin A toxicity. Signs includes anorexia, headache, vomiting, dry, itchy skin, seborrheic cutaneous lesion, fissuring at angle of mouth,
alopecia or coarsening of hair; bony abnormalities with long wavy hyperostosis of long bones, hepatosplenomegaly.19 Hepatotoxicity can result in elevated serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and/or calcium. Long term vitamin A toxicity has been associated with cirrhosis and veno-occlusive disease.20 Histopathology shows proliferation of hepatic stellate cells.20

In acute toxicity after ingestion of megadose of vitamin A, young children can develop signs of pseudo tumor cerebri with increased intracranial tension, vomiting bulging of anterior fontanelle, irritability, diplopia and stupor.19 Since there is no specific antidote of Vitamin A, prevention is essential.

A syndrome of severe congenital malformations can occur by ingestion of therapeutic doses of oral vitamin A during first trimester of pregnancy. There are characteristic craniofacial malformations, microcephaly and cardiac anomalies21 and high incidence of spontaneous abortions. Hence doses of Vitamin A above RDA must be avoided in pregnant women.

Ingestion of large doses of carotenoids, however, it is not associated with toxicity. There may be yellow discoloration of skin (carotoderma) and serum (carotenemia) which resolve spontaneously.2 At risk are children with hypothyroidism, diabetes and liver diseases.

11. VAD and public health issues

VAD is the third most common nutritional deficiency globally but is rarely seen the developed countries.15 In Southern and Southeast Asia, Africa, and South America, eye signs of VAD, including complete blindness are still seen.16 Vitamin A deficiency is considered as a public health problem when prevalence of Bitot spot is 0.5% or more in pre-school children. The prevalence of low serum retinol < 0.7 μmol/L can be used to assess severity of VAD in a population. Based on low serum retinol levels mentioned above, degree of public health problem is mild when prevalence is between 2 and 9%, moderate between 10 and 19% and severe when 20% or more.15

Globally approximately 500,000 preschool children become blind annually.22 Ophthalmic complications can be prevented by routine distribution of vitamin A to children.23 There is also evidence that vitamin A supplementation to undernourished children reduces the long-term risk of deafness among those with ear discharge.24 VAD signs can be used to assess severity of VAD in a population. Based on low serum retinol < 0.7 μmol/L can be used to assess severity of VAD in a population. Based on low serum retinol levels mentioned above, degree of public health problem is mild when prevalence is between 2 and 9%, moderate between 10 and 19% and severe when 20% or more.23

The cluster randomized DEVTA Trial conducted in India on 1 million preschool children over a period of five years showed that six monthly administration of 200,000 IU of vitamin A leads to 4% reduction in mortality (mortality ratio 0.96; 95% CI 0.89 – 1.03).25 This is in contrast to earlier claims of one-third mortality reduction in mortality (mortality ratio 0.96; 95% CI 0.89 – 1.03).25 This is in contrast to earlier claims of one-third mortality reduction in much smaller studies.26 A meta-analysis that included the DEVTA and eight previous trials showed a modest weighted average mortality reduction of 11% (95% CI 5% – 16%).27

12. Other therapeutic uses

Measles: Vitamin A has been recommended for use in children with measles in developing countries as it appears to reduce complications and mortality.28

Dermatology: Topical Retinoic acid is indicated for use in many hyperkeratotic and hyperproliferative skin disorders.29

Acute promyelocytic leukemia: All-trans-retinoic acid (ATRA, or tretinoin), a synthetic oxidative metabolite of retinoic acid, in conjunction with other standard chemotherapy, has been used in acute promyelocytic leukemia.30

References


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