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Chapter III

Vitamin A: Dietary Sources and Health Consequences

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Abstract

Vitamin A is obtained from plant provitamin A carotenoids and retinol or preformed vitamin A, from animal sources. It is liposoluble and has three active forms in the body: retinol, retinaldehyde and retinoic acid. It is found in many foods both from animal and vegetable origin, such as egg yolk, liver, whole milk, butter, broccoli, palm oil, buriti oil, tomato, watermelon, spinach, pumpkin, sweet potato, kale, cabbage, squash, carrots and others with yellow-orange and dark green colour. This bioactive compound plays an important role in many vital processes, working in the maintenance of vision, integrity of the immune system, in the formation and maintenance of epithelial tissue, bone structures and teeth, on cell proliferation and differentiation, reproduction and growth. However, vitamin A deficiency is responsible for many illnesses in human beings, among them nyctalopia, hemeralopia, xerophthalmia,

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Bitot spots, fetal malformation, reduction of smell and taste and even death. Furthermore, the low consumption of vitamin A is related to increased risk of chronic degenerative diseases such as cancer, cardiovascular problems and cataracts. Humans rely on diet to meet their daily requirements for vitamin A. The Recommended Daily Allowance (RDA) for adults (according to the US Institute of Medicine) is 900 μg and 700 μg for men and for women, respectively. Additional doses of 700 μg and 600 μg per day are recommended during pregnancy and breastfeeding, respectively. Due to their smaller body weight, infants and young children have lower DDI doses, which correspond to 400 μg for up to 6 months old and 500 μg for up to 1 year old infants and 300/400 μg per day of vitamin A are advised for children.

Keywords: Vitamin A, pro-vitamin A, retinol, daily requirements, deficiency

Introduction

Vitamina A is the appropriate denomination for retinoids with the β-ionone ring: all-trans retinol, retinal, retinil ester and retinoic acid (Gibson, 1990).

It comprises a family of essentially liposoluble compounds which are structurally related to retinol (preformed vitamin A) and are biologically active. From a nutritional perspective, carotenoids with provitamin A activity such as α-carotene, β-carotene and cryptoxanthine, which are precursors of retinol (IOM, 2001), are also regarded as vitamin A. While preformed vitamin A is found only in foods of animal origin, diet carotenoids are mainly found in fruits and vegetables. Among the almost 600 carotenoids already discovered, six of them (β-carotene, β-cryptoxanthine, α-carotene, licopene, lutein and zeaxanthine) represent more than 95% of total plasma carotenoids (Rao & Rao, 2007; Maiani et al., 2009).

Being liposoluble compounds, vitamin A has similar digestion, absorption, transport and storage processes to lipids in the human organism. Consequently, alterations in pancreatic and biliary fat digestion, reduced synthesis of transport proteins, as well as the fat contents in the diet have implications in digestion, absorption and transport of vitamin A (Ramalho et al., 2004; Teixeira, 2010).

This bioactive compound plays an important role in many vital processes, working in the maintenance of vision, integrity of the immune system, in the formation and maintenance of epithelial tissue, bone structures and teeth, on

cell proliferation and differentiation, reproduction and growth (Figure 1).(Mayo-Wilson et al., 2011).

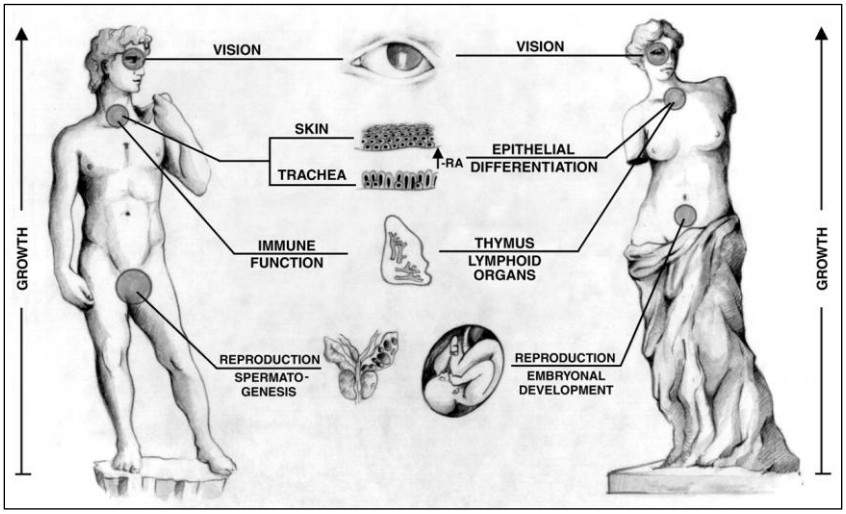

Figure 1. Vitamin A - actions on systems, tissues and functions Source: Conde, 2012.

1. Daily Requirements

Few direct studies have been conducted to determine the requirements of vitamin A. In human milk, blood and tissues, vitamin A contents are usually expressed in $mg.dL^{-1}$ or µmol.L of all-trans-retinol. Except for postprandial conditions, most of the circulating vitamin A is retinol whereas in most tissues (such as the liver), secretions (such as human milk), and other animal food sources, it exists mainly as retinyl esters, which are frequently hydrolysed before analytical detection (FAO/WHO, 2004).

A Joint FAO/WHO Expert Group, in 1967, introduced the concept of the retinol equivalent (RE), to express the vitamin A activity of carotenoids in diets, and established the following relationships among food sources of vitamin A:

1 µg retinol = 1 RE
1 µg β-carotene = 0.167 µg RE
1 µg other pro-vitamin A carotenoids = 0.084 µg RE

These results were derived from balance studies to account for the less efficient absorption and their bioconversion to vitamin A (one half for β-carotene and one fourth for other provitamin A carotenoids) (FAO/WHO, 2004).

In recent years, there has been interest in evaluating bioavailability factors by the use of quantitative stable isotope techniques. The data provided are incongruent but in general suggest a revision towards lower bioavailability estimates. Until more definitive data become available, the conversion factors above are to be used (MOH, 2005).

It has been strongly recommended that weight or molar units replace the use of IU to overcome limitations in the non-equivalence of the IU values for retinol and beta-carotenes, as well as to decrease confusion. The conversion factors to be used are:

1 IU retinol = 0.3 μg retinol
1 IU β-carotene = 0.6 μg β-carotene
1 IU retinol = 3 IU β-carotene

The content of vitamin A in food is expressed as retinol equivalents, that is, the sum of vitamin obtained from preformed retinol and carotenoids. Due to the low absorption of carotenes and to their incomplete splitting to produce retinol, it is generally accepted that (IOM, 2001; Yuyama et al., 2009):

1 μg RAE (Retinol Activity Equivalent) =	1 RE of all-trans-retinol (vitamin A) 1 μg retinol (vitamin A) 2 μg β-carotene in oil 12 μg β-carotene in mixed foods 24 μg other provitamin A carotenoids in mixed foods

The minimum daily intake of vitamin A (expressed as μg retinol equivalents: μg RE) is the mean requirement for an individual in order to prevent xerophthalmia. This consumption should account for the bioavailability of preformed vitamin A (approximately 90%) and provitamin A carotenoids from a diet that contains enough fat (for example, at least 10 g per day). The minimum required level of intake is adjusted to allow for normal growth, prevent clinical signs of deficiency, and reduce the risk of vitamin A related severe morbidity and mortality within any population. It does not allow

for frequent or prolonged periods of infections or other stresses (FAO/OMS, 2004).

Various factors affect the acquisition of sufficient amounts of vitamin A from food: the general health conditions, the total food intake, the vitamin A demand of the body, how much of the (pro)vitamin A is absorbed by the body and the efficiency of conversion of provitamin A to vitamin A (the bioavailability). Provitamin A is fat soluble, so it cannot be absorbed in the gut without fat or oil in the food. The bioavailability of provitamin A compounds also depends on food matrix and how the food is prepared. For example, more provitamin A is taken up from cooked and mashed vegetables than from raw products. Dietary deficiencies in other nutrients such as zinc and fat/oil can limit the rate of conversion, while a lack of vitamin A can, in turn, decrease iron metabolism. Hence, a balanced and diverse diet is of importance in maintaining the body's capacity to absorb provitamin A and convert it to vitamin A (Kuhnlein & Pleto 1997, Rahman et al. 2002, Brown et al. 2004, Dijkhuizen et al. 2004, MHO, 2005).

According to FAO/WHO (2001), available food composition data for most of the food consumed in the world is incomplete, outdated, or insufficient for evaluating the correct bioavailability. This is even more true for dietary changes for those who move to urban centres where most food is obtained from supermarkets where traditional products might not be sold (Graebner et al. 2004), and where green and orange vegetables, high in β-carotene, and leaves (Hels et al., 2004) disappear from the diet (Lorch, 2005).

The body reserve of the vitamin A helps offset periods of low intake or increased need resulting from infections and other stresses. Useful indicators include a plasma retinol concentration above 0.70 $\mu mol.L^{-1}$, which is associated with a relative dose response below 20% or a modified relative dose response below 0.06. For lactating women, breast-milk retinol levels above 1.05 $\mu mol.L^{-1}$ (or above 8 $\mu g.g^{-1}$ milk fat) are considered to reflect minimal maternal stores because levels above 1.05 $\mu mol.L^{-1}$ are common in populations known to be healthy and without evidence of insufficient dietary vitamin A (Wallingford & Underwood, 1986; Newman, 1994).

Taking these factors into consideration, the dietary requirement of vitamin A is well established for humans, and the dietary reference intakes (DRI) are the instrument of reference for evaluation of individual and collective adequacy. To evaluate the adequacy of nutrient ingestion the Estimated Average Requirement (EAR) must be employed. This parameter is defined as the daily ingestion level of a nutrient for which it is estimated that half (P50 or median) of the healthy individuals of the same gender and stage of life have

their requirements supplied. The Recommended Dietary Allowance (RDA) and Tolerable Upper Intake Level (UL) are established based on the EAR (Hosmer & Lemeshow, 1989; Battisti, 2008).

The established RDA covers 97 to 98% of the requirements of healthy individuals from a certain group of the same gender and stage of life, and corresponds to two standard deviations above the EAR. The RDA should be used as the aim to attain in the elaboration of dietary planing for individuals. The UL should be employed to evaluate the adequacy of nutrient ingestion, regarding the limits of risk for excessive ingestion (Teixeira, 2010).

Table 1. Estimated mean requirement and safe level of intake for vitamin A

Age group	EAR (µg/day)	RDA (µg/day)	UL (µg/day)
Infants:			
0-12 months	-	400 [AI]	600
Children:			
1-3 years	210	300	600
4-8 years	275	400	900
Males:			
9-13 years	445	600	1,700
14-18 years	630	900	2,800
19-70 years	625	900	3,000
> 70 years	625	900	3,000
Females:			
9-13 years	420	600	1,700
14-18 years	485	700	2,800
19-70 years	500	700	3,000
> 70 years	500	700	3,000
Pregnant women:			
≤ 18 years	530	750	2,800
19-50 years	550	770	3,000
Lactating women:			
≤ 18 years	880	1,200	2,800
19-50 years	900	1,300	3,000

Source: IOM (2001).

Taking into account the age and gender, Table 1 provides the estimated mean requirements for vitamin A and the recommended safe intakes. For most

values the true mean and variance are not known. It should be noted that there are no adequate data available to derive mean requirements for any group and, therefore, a recommended nutrient intake cannot be calculated. However, information is available on cures achieved in a few vitamin A deficient adult men and on the vitamin A status of groups receiving intakes that are low but nevertheless adequate to prevent the appearance of deficiency-related syndromes. The values for mean dietary requirements are derived from these, with the understanding that the curative dose is higher than the preventive dose (FAO/WHO, 1988; IOM, 2001).

1.1. Toxicity

Being a fat-soluble vitamin, retinol can be stored in the human body, primarily in the liver. Thus long term regular consumption of large amounts of vitamin A can result in toxic symptoms (Yuyama, 2009; Mayo-Wilson, 2011).

Retinol is toxic in acute and chronic forms. In acute toxicity, high doses of retinol (above 300 mg in a single dose for adults) cause nausea, vomiting, headache, increased cerebrospinal fluid pressure. These symptoms disappear in a few days. Extremely high doses can be fatal (Oliveira, 2006; Mayo-Wilson, 2011).

Chronic vitamin A toxicity is the most common cause of concern. Usual and prolonged ingestion of higher doses than 7.5 to 9.0 mg/day for adults affect the central nervous system (causing nausea, ataxia and anorexia, headache), the liver (resulting in hepatomegaly, hyperlipidemia and histological alterations), the bones (causing arthralgia, thickening of long bones, hypercalemia and calcification of soft tissues) and the skin (excessive dryness, cracked skin, skin desquamation, and alopecia) (Penniston & Tanumihardjo, 2006; Yuyama et al, 2009).

1.2. Factors Affecting Requirements

Dietary fat performs an important role in the absorption of ingested vitamin A. Dietary vitamin A is digested in mixed micelles and absorbed with fat. Studies show that increasing the level of fat in a low fat diet can improve retinol and carotene absorption. For better carotenoid absorption, dietary fat must be consumed alongside with provitamin A compounds (MHO, 2005).

The matrix of the food affects the biovailability of carotenoids and therefore affects intestinal absorption. For example, the increase of β–carotene concentration, in serum, has been observed to be significantly lower when individuals ingested carrots than when they received the same amount of vitamin from β–carotene supplement. The processing of food also greatly affects the absorption of carotenoids. Cooking of carrot and spinach also greatly improved absorption (Yuyama et al., 2009).

Malabsorption of vitamin A can occur with diarrhea and intestinal infections such as gastroenteritis and respiratory infections, and also associated with intestinal parasitism (MHO, 2005).

2. Dietary Sources

Foods that provide preformed active vitamin A are from animal sources, being the richest: liver and fish liver oils (especially), egg yolk, human milk, whole milk, and other dairy products (Figure 2). Preformed vitamin A is also used to fortify processed foods, which may include sugar, cereals, condiments, fats, and oils (Yuyama et al., 2009).

Food derived from plants contains precursors of vitamin A, which are the carotenoids, particularly β-carotene, with 100% provitamin A activity. These are found in green leafy vegetables (e.g. spinach, amaranth, and young leaves from various sources), yellow vegetables (e.g. pumpkins, squash, and carrots), and yellow and orange non-citrus fruits (e.g. mangoes, apricots, and papayas). Red palm oil produced in several countries worldwide is especially rich in provitamin A (Haskell, 2013). Foods containing provitamin A carotenoids tend to have less biologically available vitamin A but are more accessible than animal products. It is mainly for this reason that carotenoids provide most of the vitamin A activity in the diets of least developed countries (FAO/OMS, 2004).

Carotenes from the diet are the main form of access to vitamin A, and it is estimated that around 68% and 82% of vitamin A are obtained from this source in the world and in developed countries, respectively (Teixeira, 2010).

In theory, the world's food supply is enough to meet global requirements for vitamin A. However, there are large differences in the availability of sources and in per capita consumption of the vitamin among different countries, age categories, and socioeconomic groups. Vitamin A deficiency is a global public health problem largely due to inequitable food distribution among and within countries (UNICEF, 2007).

Some contents of vitamin A in foods are listed in Table 2.

Table 2. Vitamin A content in food

Food	Weight [g]	Vitamin A [ER]
Cooked liver	100	10,700
Cooked chicken	100	4,900
Cod-liver oil	13.6	4,080
Raw carrot	72	2,025-3,800
Cooked carrot	76	1,300-1,900
Baked sweet potato	60	1,310
Mango	207	805
Cooked spinach	95	739
Raw broccoli	44	704
Cooked cabbage	90	502
Cooked beet	72	367
Tomato juice	242	283
Red chili	37	212
Raw spinach	30	202
Fresh apricot	70	183
Cooked shellfish	100	171
Cooked broccoli	92	174
Dry plum	85	169
Romaine lettuce	56	146
Tomato sauce	123	120
Butter	14.2	109
Cheddar cheese	28.4	86
Cooked egg	48-50	84
Cooked shrimp	100	66
Raw tomato	90	56
Papaya	140	39

Source: Hands, 2000.

3. Symptoms of Deficiency

Being important in low amounts for human metabolism, vitamin A is necessary for adequate vision function, maintainance of epithelial cell

integrity, immune function, growth and development, gene expression, antioxidant defense and cell reproduction (Greaves et al., 2012).

The vitamin A deficiency (VAD) is not easily defined. Subclinical vitamin A deficiency is defined as the sufficiently low tissue concentration of the vitamin to cause adverse consequences to the health, even though there is no evidence of xerophthalmia. However, due to recent findings, the World Health Organization (WHO, 1994) included the clinical and subclinical deficiencies (low, moderate and severe degree of deficiency) in the concept of Vitamin A deficiency, as well as any situation in which hipovitaminosis can have adverse health effects (Cristóvão et al., 2005).

Deficiency of this micronutrient can be classified as primary or secondary. Primary VAD results from a negative balance between dietary intake and retinol and carotenoid requirements. Secondary VAD can result from a number of patogenic alterations such as lipid malabsorption, pancreatic or billiary insufficiency, abetalipoproteinemia, hepatopathies, protein-energy malnutrition and zinc deficiency (Teixeira, 2010).

Regarding biochemical markers, WHO recommends that whenever the deficiency is restricted to the presence of clinical symptoms, the term "clinical deficiency" or "xerophthalmia" should be employed, with a threshold level of serum under or equal to 0.70 µmol/L, to diagnose vitamin A deficiency in children. When prevalence of vitamin A deficiency comprises at least 10% of a population, it is considered a serious public health problem (Cristóvão et al., 2005, Tansuğ et al, 2010).

As histological marker, conjunctival impression citology is characterized by the presence of increased planar cells and significant reduction of mucin producing cells in cases of vitamin A deficiency (WHO, 1996, Oliveira, 2006).

WHO defines it as tissue concentrations of vitamin A low enough to have adverse health consequences even if there is no evidence of clinical xerophthalmia. In addition to the specific signs and symptoms of xerophthalmia and the risk of irreversible blindness, nonspecific symptoms include increased morbidity and mortality, poor reproductive health, increased risk of anaemia, and contributions to slowed growth and development. However, these nonspecific adverse effects may be caused by other nutrient deficits as well, making it difficult to attribute non-ocular symptoms specifically to VAD in the absence of biochemical measurements reflective of vitamin A status (FAO/WHO, 2004).

Vitamin A deficiency (VAD) constitutes one of the nutrition deficiencies that have the highest effects on the health status of biologically vulnerable groups such as children and pregnant women (Figure 3). It is considered a

severe public health problem worldwide, especially in underdeveloped countries, with severe consequences to child health, such as: reduction of growth and development, eye disorders, immune deficit and increased morbimortality associated to respiratory infections, diarrhea and measles (Martins, 2007, Azevedo et al., 2010).

It is estimated that 250 million preschool age children in the world have subclinical VAD and that 4.4 million have xerophthalmia, being Asia, Africa and Latin America, the highest prevalence regions (Figure 3). In the American continent, it is estimated that 8.2 million children have vitamin A deficiency and 2.2 million of these cases are registered in Brazil (Ramalho, 2002, West, 2002, Brasil, 2012).

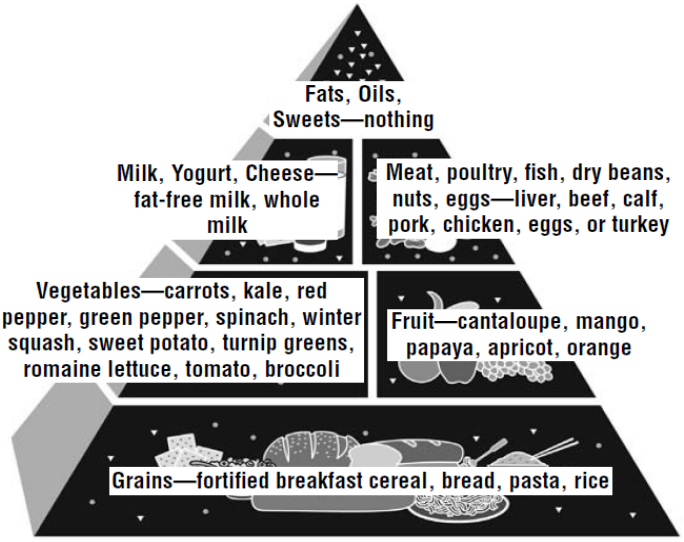

Figure 2. Where to find Vitamin A in the Food Guide Pyramid.

The relationship between vitamin A deficiency and mortality was initially observed in 1930, when it was found that vitamin suplemmentation significantly reduced mortality of pacients with measles (Ellison, 1932). The metanalysis done by Fawzi et al. (1993) with ten controled studies showed that the therapeutic administration of vitamin A contributed to reduce mortality in children that lived in developing countries. Administration of vitamin A to children that developed pneumonia before or during hospitalization reduced mortality about 70%, compared to the control group. This finding suggests that vitamin A supplementation reduced the severity of pneumonia in those

pacients, in a similar way found in studies which report the decrease of severity of pneumonia and diarrhea in pacients with measles that were treated with vitamin A, compared to those that were given placebo (Cristóvão et al., 2005).

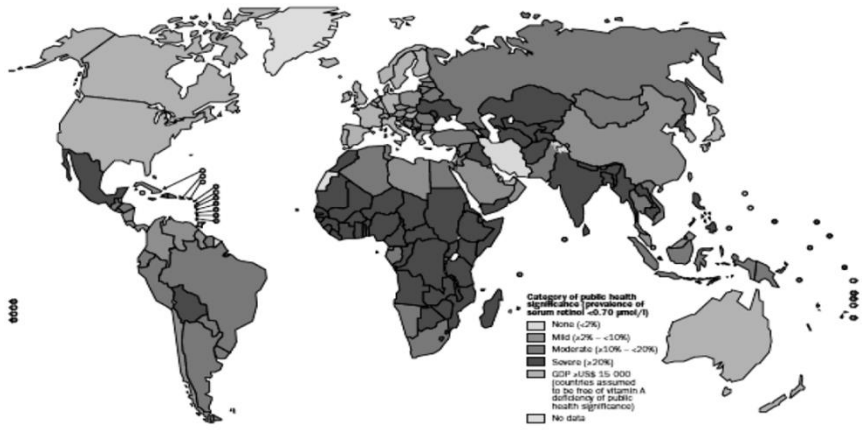

Figure 3. Classification of VAD public health problem [plasma retinol <0.70 µmol/L] worlwide, according to estimates from 1995 to 2005. Source: WHO (2009).

3.1. Clinical Signs and Symptoms of Vitamin A Deficiency

Among the diverse alterations that follow the deficit of this micronutrient, are included (Sommer, 1995, Rice et al, 2004, Teixeira, 2010):

- Vision: keratomalacia, dry eyes, with ulcerations and conjunctive and corneal xerosis as the initial signs. Night blindness, the most known, is one of the first symptoms of vitamin A deficiency. Extreme difficulty of vision, including total blindness are the most severe consequences of the deficiency;
- Respiratory system: the airway epithelium is altered, keratinization, resulting in an increased susceptibility to infections. Pulmonary elasticity may also decrease, impairing breath;
- Skin: keratinization and skin dryness lead to erruption of papules surrounding the sebaceous follicles, mainly at the extremities of the limbs;

- Genito-urinary system: vitamin A deficiency can also lead to kidney stone formation. The epithelium of the urinary tract becomes rough, favoring crystal deposition and formation of stones. There are also modifications in sperm production, testicle degeneration, abortions, abnormalities and fetal deaths;
- Digestive system: alterations in the intestinal epithelium are observed, as well as metaplasias in the epithelium of the pancreatic ducts, which would be responsible for the diarrhaeas attributed to vitamin A deficiency;
- Sudoriferous glands: may undergo atrophy and keratinization. Modification of sweat may alter other smells of the body;
- Bones: in animals, experimental vitamin A deficiency leads to increased porosity and thickening of the bones;
- Nervous system: smell, taste and hearing alterations can occurr. Nerve lesions and increased production of cerebrospinal fluid along with hydrocephaly have been reported;
- Blood: red blood cell production can be reduced.

3.2. Age and Sex

Vitamin A deficiency can occur in individuals of any age. However, it is a more harmful and potentially fatal public health problem for children under 6 years of age. The blindness is most prevalent in children under 3 years of age (Sommer, 1995).

Infants and children have increased vitamin A requirements to support rapid growth and to help them to combat respiratory and gastrointestinal infections (Beaton, 1993, WHO, 2011). The increased mortality risk from concurrent infections extends at least to 6 years of age and is associated with both clinical and subclinical VAD. There is little information regarding the health consequences in school-age children (Sommer, 1995).

Vitamin A deficiency has now become evident in women of reproductive age and has negative consequences on their health status (Scrimshaw & San Giovanni, 1997). In pregnant women it is associated with night blindness, severe anaemia, wasting, malnutrition, and reproductive and infectious morbidity, and increased risk of mortality 1-2 years following delivery. VAD reduces lymphocyte response, and also leads to reduced levels of secretory IgA in mucous membranes and therefore weakens the local barriers to infection. As a result, vitamin A deficient women were found to be more

susceptible to illnesses of both infectious, such as frequent infection of mucous surface of hollow viscera, and non-infectious (eclampsia, pre-eclampsia, premature rupture of membrane) diseases. (Mulu et al, 2011)].

There is no consistent, clear indication in humans of a sex differential in vitamin A requirements during childhood. Growth rates, and presumably the need for vitamin A, from birth to 10 years for boys are consistently higher than those for girls. In the context of varied cultural and community settings, however, variations in gender-specific child-feeding and care practices are likely to subsume a small sex differential in requirements to account for reported sex differences in the prevalence of xerophthalmia (FAO/WHO, 2004).

3.3. Morbidity and Mortality

The consequences of VAD are manifested differently in different tissues. Although ocular symptoms and signs are the most specific indicators of VAD, they occur only after other tissues have impaired functions that are less specific and less easily assessed (Sommer, 1995).

The prevalence of ocular manifestations is accepted to far underestimate the magnitude of the problem of functionally significant deficiency. In children, subclinical deficiency, like clinical deficiency, increases the severity of some infections, particularly diarrhea and measles, and also the risk of death (Beaton, 1993, FAO/WHO, 2004).

There are differences in the relation between incidence and severity of infectious morbidity of various etiologies and vitamin A status. A great deal of evidence supports an association of VAD with severity of an infection once acquired, except for respiratory diseases, which are non-responsive to treatment (Bhandari et al., 1994, FAO/WHO, 2004).

Infectious diseases depress circulating retinol and contribute to vitamin A depletion. Enteric infections may alter the absorptive surface area, compete for absorption-binding sites, and increase urinary loss (Solomons and Keusch, 1981, Feachem, 1987, Alvarez et al., 1995).

Another important factor that affects many aspects of vitamin A metabolism is the severe protein–energy malnutrition, and even when some retinyl ester stores are still present, malnutrition - often coupled with infection - can prevent transport-protein synthesis, resulting in immobilization of existing vitamin A stores (FAO/WHO, 2004).

Based on the above, in summary, vitamin A deficiency affects vulnerable populations throughout critical stages of life, with higher incidence of disease in young children and pregnant women. Successful efforts to control and reduce vitamin A deficiency have the potential to improve the health and well-being of women and children around the world and to reduce the global burden of disease associated with this nutritional risk factor.

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