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Chapter

Vitamin A in Health and Disease

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Abstract

Vitamin A refers to a group of related compounds with all-trans retinol biological activity and includes retinol, retinal, retinoic acid as well as the retinyl esters. Dietary source of vitamin A ranges from animal-based or plant-based foods, fortified food products and supplements. The vital biological roles of vitamin A compounds include normal cell growth, cell differentiation, vision and immunology. Vitamin A status is monitored to prevent occurrence of both subclinical deficiency and toxicity. Vitamin deficiency or excess is determined through the measure of vitamin A status. Prolonged vitamin A intake at high doses is shown to be toxic, which leads to various health symptoms. Xerophthalmia, a dry eye condition is the most severe clinical effects known to be caused by vitamin A deficiency. The resulting deleterious effects on human health led to efforts of supplementation, food fortification and dietary diversification in combating vitamin A deficiency. In brief, this chapter covers on vitamin A, with focus on its general information, dietary recommendations, biological roles, vitamin A status assessment, deficiency or excess effects to human health as well as the prevention measures.

Keywords: vitamin A, biological roles, deficiency, excess, human health

1. Introduction

Vitamin A in health and disease chapter intends to introduce general information of vitamin A with specific focus mainly on its dietary recommendations and its importance to human health. In line with this, continuous monitoring of vitamin A status that determines deficiency or toxicity state that could significantly affect human health along with prevention efforts is also described.

Vitamin A is a fat-soluble vitamin and also comprises of a group of unsaturated nutritional organic compounds. These compounds include preformed vitamin A that exist in the form of retinol (alcohol), retinal (aldehyde), retinoic acid (irreversibly oxidized form of retinol) and several pro-vitamin A carotenoids (mainly β–carotene). The preformed vitamin A can only be obtained from the diet in food of animal origin and is the most abundant form of vitamin A in the human body. Retinol is a yellow fat-soluble substance, an absorbable form of vitamin A present in animal food sources. This chemical structure makes it poorly soluble in water but easily transferable through membrane lipid bilayers. Retinol is an alcohol and is known to be unstable. Vitamin A is mainly found in human tissues in the form of retinyl esters, which explains why the vitamin is commercially produced and administered as esters of retinyl acetate or palmitate. Retinyl esters will subsequently be converted into retinols in the small intestine [1, 2]. The pro-vitamin A comes from plant-derived

foods primarily in oils, fruits and vegetables. β-Carotene is the major source of vitamin A precursor from plants and is represented as two connected retinyl groups. The molecules contribute to the body's total vitamin A level. All forms of vitamin A have a β-ionone ring, which is attached to an isoprenoid chain (retinyl group). Both of these structural moieties are essential for the vitamin to exert biological activity. The β-ionone ring containing carotenoids include α-carotene, β-carotene and the xanthophyll β-cryptoxanthin [2].

Vitamin A can be found in a variety of foods. The bioavailability of carotenoids in food is variable because the efficacy of metabolic processes that convert carotene into retinol varies from one person to another. **Table 1** shows important dietary sources of vitamin A. Foods rich in retinol include meat, butter, retinol-enriched margarine, dairy products and eggs, while foods rich in β-carotene include vegetables and fruits (e.g. sweet potatoes, carrots, dark-green leafy vegetables, sweet red peppers, mangoes, melons). Several processed foods have been fortified with vitamin A and are good sources of the vitamin, such as cornflakes, malted milk powder and milk powder [2–4]. Foods containing pro-vitamin A carotenoids tend to have less biologically available vitamin A but are more affordable than animal products especially in the diets of economically deprived populations.

Retinol, in the form of retinyl esters, and pro-vitamin A carotenoids enter the human body as a component of nascent chylomicrons secreted into the lymphatic system. Most dietary retinol (in chylomicrons and chylomicron remnants) is taken up by the liver, which is the major site of retinol metabolism and storage. Once circulating retinol is absorbed from the intestine, it will bind primarily to a protein

Food category	Vitamin A (μg retinol equivalent/100g)
Meat/poultry/fish	
Liver (ox/beef, chicken)	9000–16,000
Egg, whole (duck, hen)	208–304
Chicken, duck (thigh)	50–69
Fish, mackerel, Indian/Spanish	8
Vegetables	
Carrot, raw	835
Sweet potato	709
Spinach	469
Broccoli	31
Fruits	
Mango	54–214
Papaya	55–193
Apricot	96
Watermelon	28–68
Processed Food	
Butter	200–684
Cheddar cheese	117–265
Full cream milk powder	400
Malted milk powder	711

Table 1.
Dietary sources of vitamin A and retinol activity equivalences (adapted from [5, 6]).

called retinol-binding protein (RBP). The RBP will enter and leave the liver several times daily due to its lipophilic properties in a process known as retinol recycling. The retinol will bind to a cellular RBP (CRBP-I or CRBP-II) and can then be esterified by enzyme lecithin: retinol acyltransferase (LRAT), which enables the vitamins to be interconvertible, i.e. the stored ester and circulating retinol form. The storage efficiency and retinol catabolism are dependent on vitamin A status. Low retinol stores are associated with reduced storage efficiency and decrease the absolute catabolic rate [2].

To express the vitamin A activity of carotenoids in diets on a common basis, a concept of the retinol equivalent (RE) was introduced [7]. Based on this concept, the relationships among food sources of vitamin A were established as shown below:

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

A new term, retinol activity equivalent (RAE), was introduced in order to express the activity of carotenoids after taking into account new research on vitamin A activity of carotenoids [8, 9]. Specific carotenoids/retinol equivalence ratios are defined for pro-vitamin A carotenoids, which account for the less efficient absorption of carotenoids and their bioconversion to retinol. Recent work has shown that the absorption of carotenoids, the vitamin A precursors, is only half of as much as that previously considered. Institute of Medicine established the following conversion factor equivalents:

1 μg retinol	=	1 μg RAE
1 μg β-carotene in oil	=	0.5 μg RAE
1 μg β-carotene in mixed foods	=	0.083 μg RAE
1 μg β-carotene and other pro-vitamin A carotenoids in mixed foods	=	0.042 μg RAE

The use of SI units (weight and molar) is strongly recommended to replace the use of IU in many databases to decrease confusion and overcome limitations in the nonequivalence of the IU values for retinol and β-carotenes. The conversion factors to be used are as follows:

1 IU retinol	=	0.3 μg retinol
1 IU β-carotene	=	0.6 μg β-carotene
I IU retinol	=	3.0 μg β-carotene

2. Biological roles of vitamin A

Vitamin A is an essential micronutrient required in small amounts by human throughout the life cycle to perform multiple metabolic functions. It is important for growth and development, the maintenance of immune function and maintenance of epithelial cell integrity, good vision, reproduction as well as lipid metabolism. Vitamin A is also an important antioxidant, a property shared with vitamins

E and C, respectively [3]. New biological functions of vitamin A such as lipid metabolism, insulin response, energy balance and the nervous system are continuously being discovered.

2.1 Vitamin A and health importance

Vitamin A has long been known to play a critical role in vision. Night blindness or reduced vision ability under dim light is a very early and purely subjective symptom of vitamin A deficiency (VAD). In the eye, the 11-cis retinal binds to protein, term opsins, to form both the rhodopsins (rods) and iodopsins (cones) visual pigments [10]. Light that enters the eyes will isomerise the bound 11-cis retinal to all-trans form which initiates excitation of the photoreceptor cell. This isomerisation reaction will trigger nervous signal and passes along the cranial 'optic nerve' destined for the visual centre of the cerebral cortex that translates into a picture [11, 12]. A vitamin A metabolite, retinoic acid (RA), is essential for the normal functioning of the immune system [13]. Retinol and its derivatives function as an immune enhancer that potentiates the antibody response; at the same time it maintains and restores the integration of all mucosal cells and their functions. Retinols are also required for the development of leukocytes that play a major role in mounting an immune system. The major site of vitamin A action in the immune response is thought to be the T helper cell and T lymphocytes cell. The retinol derivative '4-hydroxyretinoic acid' rather than retinoic acid is important in this aspect [14].

Along with its role in vision and immune system, vitamin A has also been shown to be actively involved in the production of red blood cells, which are derived from stem cells that depend upon retinoid for their proper differentiation. Vitamin A also appears to facilitate the mobilisation of iron stores to the developing erythrocytes where it is incorporated into haemoglobin, the oxygen carrier complex protein [15]. In addition, vitamin A (retinol, retinoic acid, all-trans retinal) is an important signalling molecule that affects gene expression and is called 'retinoid-controlled genes' which are involved in the differentiation and development of foetal and adult tissues, stem cell differentiation, apoptosis, support of reproductive and immune functions and regulation of lipid metabolism and energy homeostasis [16]. Retinol and retinoic acid also play a vital part in the development of human embryo and differentiation of three germ layers and propagation of the signalling process in the formation of the neural tube, organogenesis and development of limbs during embryogenesis. There are two main types of high-affinity receptor for trans- and cis-retinoic acid isomers within the nucleus cells of vertebrates including mammals. Each set of these receptors has six different domains which are involved in gene expression [17].

In terms of skin health, the isoform retinoic acid will switch on genes that differentiate immature skin cells into mature epidermal cells. Vitamin A and its metabolites have also been shown to improve photo-aged and chronologically aged skin pathologies. They promote the deposition of new collagen fibres and prevent degradation occurring in such skin types [11]. Growth hormone is a peptide hormone that stimulates growth (anabolic metabolite), cell reproduction and cell regeneration in humans and other animals. Growth hormone is a 191-amino acid, single-chain polypeptide that is synthesised, stored and secreted by the somatotropic cells within the lateral wings of the anterior pituitary gland. The availability of vitamin A is necessary for expression of many genes including those human growth hormones [11].

Studies showed that vitamin A in the form of retinol is required for maintenance of adult mammalian spermatogenesis. Spermatogenesis is the production and development of sperm. It is a process which sperm cells undergo a series of cellular changes and divisions in order to fully develop. The cell begins as a spermatogonium and the undeveloped diploid sperm cell and ends as four spermatids. These

spermatids form fully developed sperm cells that comprise semen. Retinoid acid is an essential regulator of gametogenesis both in male and female gametes, such that they can enter meiosis [18]. Antioxidant activity is another identified vital role, where the presence of vitamin A or β-carotene in small doses showed anticancer effect. It appears to stem from its ability to scavenge for reactive oxygen species (ROS) and can improve immune function in addition to eliciting an anti-proliferative effect through the retinoic acid receptor (RAR) and retinoid X receptor (RXR). ROS are the most important free radical in biological system and harmful by-products generated during the normal cellular functions. In this way, they can block certain carcinogenic processes and thus inhibit tumour cell growth [11, 19].

3. Assessing vitamin A status

Vitamin A status of a specific population is important to better understand health status of the community in that particular area. VAD can lead to many health consequences, with children, pregnant and lactating women known to be the prominent groups suffering from VAD in many low-income countries [20]. Its prevalence of deficiency in a population is assessed by specific indicators/biomarkers [21].

3.1 Indicators to assess vitamin A status

There are several indicators/biomarkers to detect VAD. The 'gold standard' method to assess vitamin A status is through the direct measurement of liver reserves of vitamin A through biopsy, since in human, vitamin A is stored abundantly (>90%) in the liver [22]. A study in average-weight individuals for 4 months had shown that an estimated cut-off at 0.07 μmol/g liver was able to protect them from any clinical signs of VAD [23]. Unfortunately, this method is not feasible for population evaluation [24, 25]. Therefore, other various methods are being proposed to assess and monitor VAD based on their different aspects. The two different ways include biological (clinical, functional, histological) and biochemical indicators [26]. In 2010, liver reserves of vitamin A were plotted against the commonly used indicators to define the range of liver reserves associated with the specific indicators. It was later updated in 2015 as presented in **Figure 1** [27].

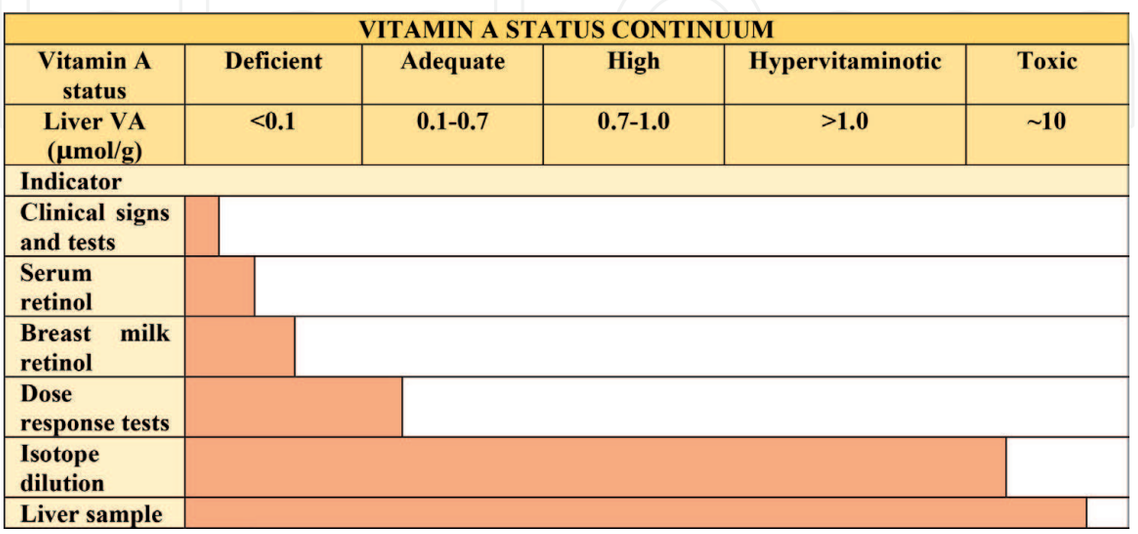

Figure 1.
The definition of vitamin A status assessed by using vitamin A indicators associated with vitamin A concentration in the liver. In 2010, 0.7–1 μmol/g was considered adequate, but this range is considered high (updated in 2015) until more biologically meaningful data are generated.

3.1.1 Biological indicators

Biological indicators consist of clinical, functional and histological components. The clinical indicators are xerophthalmia where it consists of two words, 'xeros' (dry) and 'ophthalmia' (eye), which refers to specific eye diseases caused by VAD [28]. It is classified into several groups with night blindness being the earliest ocular sign of VAD. The xerophthalmia classifications and its associated criteria of public health problems by WHO are highlighted in **Table 2**.

Xerophthalmia classifications	Symbol	WHO criteria	Epidemiological aspect	Method of assessment
Night blindness	XN	>1%	Difficult for children below 2 years, highly specific, less sensitive	Survey/questionnaire
Conjunctival xerosis	X1A	Not applicable	Not a reliable indicator of prevalence	Clinical examinations
Bitot's spot	X1B	>0.05%	Common in men, mostly occur in preschool children. Usually associated with history of X1A and night blindness	
Corneal xerosis	X2	>0.01%	A mild superficial haze due to obvious corneal change	
Corneal ulceration/ keratomalacia (<1/3 corneal surface)	X3A	>0.01%	Rapidly induced by VAD and measles infection	
Corneal ulceration/ keratomalacia (≥1/3 corneal surface)	X3B	>0.1%	Irreversible stage even with supplementation	
Corneal scar	XS	>0.05%	Bilateral with onset before 5 years	
Xerophthalmic fundus	XF	Not applicable	Rare manifestation of VAD	

Table 2.
Xerophthalmia classifications and its associated criteria of public health problem as per WHO (adapted from [57]).

3.1.1.1 Functional indicators

Night blindness (XN) or poor adaptation to the dark is a functional indicator of VAD, which is assessed by taking a history from mothers and both pregnant and lactating women. The cut-off point to indicate the deficiency in mothers and children (age 24–71 months) is ≥1% report history of night blindness [29]. Night blindness occurs if vitamin A is seriously depleted since it is responsible for vision under very low illumination [30].

3.1.1.2 Clinical indicators

Signs of chronic, long-standing VAD of xerophthalmia are conjunctival xerosis (X1A) and Bitot's spots with conjunctival xerosis (X1B). In general, a very bright torchlight in natural light is used to examine the eyes [29]. Conjunctival xerosis or drying can occur in both eyes where eyes turn dry and non-wettable with wrinkle presence at the temporal conjunctiva [31, 32]. Bitot's spots are the accumulation of fine white foamy cheesy material comprising keratin, on the conjunctival surface [28].

Signs of acute, sudden onset of VAD are corneal xerosis (X2), corneal ulceration with xerosis (X3A), keratomalacia (X3B) and xerophthalmia fundus (XF). Corneal xerosis (X2) is drying of the cornea due to the lack of mucus and tears (wetting agent) because glands in the conjunctiva are no more functioning normally [33]. Lesions on the cornea become denser, and stromal oedema starts to develop during corneal xerosis. The cornea appears to be granular, rough and blurry when examined using a hand light [32]. At this stage, treatment with vitamin A will heal the eyes within 1 to 2 weeks without leaving any scars. Corneal ulceration with xerosis (X3A) is permanent destruction of all or some parts of the corneal stroma which are prominent. Ulcers may be shallow but usually become deep if it penetrates into the cornea. Vitamin A therapy can cure superficial ulcer, leaving small scars, while deeper ulcers and perforations form dense scars [28].

Keratomalacia (X3B) means softening of the cornea, and it is a rare stage of xerophthalmia. The cornea may become thickened and melt away due to a progression of necrosis or death of tissue, affecting the collagen in the cornea [32]. Blindness is usually inevitable, although other eyes and the lives of children can be instantly saved by vitamin A therapy. Keratomalacia is also usually associated with secondary eye infections but can be treated with an antibiotic [28]. Xerophthalmia fundus (XF) is the appearance of small yellowish lesions on the fundus of the eye, which occurs due to the loss of pigment from the retinal pigment epithelium caused by VAD. The lesions are sometimes accompanied by blind spots or scotomas, congruent with their distribution on the retina [34]. The healing or end result of corneal ulceration and keratomalacia is corneal scars (XS). Scars are left on the cornea with varying densities, known as staphyloma (permanent bulging of the damaged cornea) or phthisis bulbi (shrunken globe), whereby the contents of the intraocular are gone and can lead to blindness [28].

3.1.1.3 Histological indicators

The morphological changes of epithelial cells from the conjunctiva surface can be assessed using a piece of filter paper. Normal conjunctiva cells show an abundance of mucin-secreting goblet cells and small epithelial cells. However, if there is a deficiency in vitamin A, the goblet cells and mucin droplets will reduce, and the epithelial cells become enlarged, separated and flattened [29]. Histological indicators include conjunctival impression cytology (CIC) and impression cytology with transfer (ICT). Assessing VAD using both techniques requires standard pore size filter paper, slides and a simple light microscope. The method involves gently applying a filter paper on the surface of the conjunctiva for 2–3 seconds, and after removal, it is placed in fixative and stained to differentiate the goblet cells from the endothelial cells. The eye is classified as normal or abnormal based on the number of goblet cells, which is counted under a microscope [35]. The differences between the two techniques are ICT only require single staining while CIC include extra processing steps for fixing, staining and mounting specimens. Comparatively, the CIC technique is more efficient in transferring cells of high quality from filter paper to slide [29].

3.1.2 Biochemical indicators

Biochemical indicators include serum and breast milk retinol concentrations, relative dose response (RDR) test, modified relative dose response (MRDR) test and isotope dilution (ID) assay.

3.1.2.1 Serum retinol concentrations

Serum retinol concentrations are among the most common method used to identify populations at risk of VAD [36]. They are determined using high-performance liquid chromatography (HPLC). The current cut-offs for VAD are <0.70 μmol/L, while severe VAD is classified below 0.35 μmol/L [21]. However, this indicator is affected by infections [37], inflammation and inadequate intakes of protein, zinc or energy, which are needed for retinol-binding synthesis [38]. Therefore, before using serum retinol concentration to assess VAD in a population, these factors should also be taken into consideration. In addition, serum retinol concentrations are homeostatically controlled over a broad range of body store and only decline when the liver reserves are very low [39]. Serum retinol concentrations should be used in conjunction with another biological indicator or when four or more of the following risk factors are detected in the population being assessed [40]. These risk factors include:

a. Infant mortality rate and under 5 years old mortality rate are >75 of 1000 and >100 of 1000 live births, respectively.

b. Less than 50% of children of 12–23 months old have full immunisation coverage.

c. The prevalence of breastfeeding in 6-month-old infants are <50%.

d. Among 75% of children (1–6 years old) have median dietary intakes <50% of the recommended safe levels of intake.

e. The prevalence of 2-week period of diarrhoea is ≥20%.

f. Fatality rate of measles cases is ≥1%.

g. More than 50% of women (15–44 years old) have no formal schooling.

h. Less than 50% of households has a safe water source (e.g. boiled, treated, filtered, properly stored).

3.1.2.2 Breast milk retinol concentrations

Breast milk retinol concentration is a unique indicator in lactating women. It has also been proposed as a measure of the population status of vitamin A, since the probability of infant and children at risk of VAD is very high if the lactating women are of a community with marginal vitamin A status [41]. Vitamin A deficiency is considered a moderate public health problem if the prevalence of inadequate milk retinol concentrations (≤1.05 mmol/L or ≤8 mg/g milk fat) is ≥10–<25% [29]. The breast milk samples are easier to obtain, and the concentration of retinol in milk can be determined after saponification by HPLC, similar to those used to determine serum retinol [42].

3.1.2.3 Relative dose response test (RDR)

The test principle of the RDR is on the basis that when vitamin A undergoes depletion, apo-retinol-binding protein (apo-RBP) accumulates in the liver. In this test, a challenge dose of retinyl ester is given to the subject, and blood samples are withdrawn prior to dosing (baseline) and 5 hours after dosing. The retinol from retinyl ester will bind to the excess RBP and is released into serum as holo-retinol/retinol-binding protein complex (holo-RBP-retinol complex). A percentage change is measured as per Eq. 1 where RDR ≥ 20% indicates VAD [35].

$$RDR\,(\%) = \frac{[A5] - [A0]}{[A5]} \times 100 \quad (1)$$

where, [A5] is the serum retinol concentration at 5-hr post-dosing; and [A0] is the serum retinol concentration just before dosing (baseline).

3.1.2.4 Modified relative dose response test (MRDR)

MRDR is a modified test of RDR using 3, 4-didehydroretinyl acetate (DRA) as the challenge dose, followed by a high-fat snack to ensure adequate absorption. In this method, a single blood sample is taken after 4 to 7 hours dosing [43]. In parallel to retinyl esters, DRA is hydrolysed to 3, 4-didehydroretinol (DR) within small intestine, taken up by enterocytes and esterified to form various didehydroretinyl esters. The esters are de-esterified to form DR in the liver, which can bind to apo-RBP and be released into serum or can be re-esterified and stored in stellate cells. The only difference between DR and retinol is the presence of a double bond located in the 3–4 position on β-ionone ring of DR. This structural difference can be separated using HPLC due to their difference in polarity. The MRDR value, which is used to indicate liver reserves, is the ratio of DR to retinol in serum [27]. The ratio of 3, 4-didehydroretinol (DR) to retinol is calculated, and the value of ≥0.06 indicates VAD in children [44]. The MRDR test has been widely used to diagnose a subclinical vitamin A status.

3.1.2.5 Isotope dilution (ID) assay

Of all the indicators available, the most accurate method to indirectly measure the vitamin A storage in the liver known till now is the isotope dilution assay [45–47]. Isotope dilution assay could detect a full range of vitamin A content in the body from deficient state up to the toxic level [48]. This test involves blood sample collection before and after the administration of a stable isotope tracer (deuterated or ^{13}C-labelled retinyl acetate) at an appropriate equilibration period. The variations in the equation and assumptions used in the calculation are dependent on the study design based on the population assessed. The method of mass spectrometry used, the dosage size given to the subjects and the time allowed for equilibration were also taken into consideration when calculating the total body reserve in the ID test [41]. The ID assay is determined as shown in Eq. 2.

$$(F_a \times a) + (F_b \times b) = (F_c \times c) \quad (2)$$

where:
a is the amount of dose absorbed and stored (dose × absorption rate).
b is the baseline total body reserves of vitamin A.

c is the total body reserve in μmol after the dose (c = a + b).

$$F = \frac{R}{R+1} \quad \text{and } R \text{ is } {}^{13}C/{}^{12}C \tag{3}$$

where F_a, F_b and F_c are the abundance of isotopes [^{13}C/total C; At %/100; R/(R + 1)] from dose, baseline serum and serum after the dose.

4. Effects of vitamin A deficiency or toxicity on human health

Routine monitoring of vitamin A status serves as an important measure in the determination of toxicity due to excessive intake or deficiency in a population. Under circumstances where dietary consumption does not meet the recommended criteria, this could lead to vitamin deficiency or toxicity depending on whether the vitamin consumption is insufficient or in excess, respectively. Various health implications have been reported as a consequence of both vitamin deficiency and excess, as discussed below.

4.1 Vitamin A deficiency (VAD)

Dietary source of vitamin A is generally available in various forms, of which the preformed retinol from animal-based source (eggs, liver, dairy) is the most bioavailable form of vitamin A. Plant-based food sources are rich in pro-vitamin A; however, populations that are dependent solely on these sources are at higher risk of VAD since its absorption is reliant on various factors [49, 50]. VAD is commonly associated with decreased immunity and higher risk of night blindness [51]. It is worthwhile to note that this deficiency is highly prevalent in countries with an alarming increase of diabetes especially among those of lower income group in United States as well as Asian developing countries [51, 52].

Vulnerability to VAD differs according to specific life stages that include infancy, childhood and pregnancy. VAD in neonates is highly related to insufficient vitamin A in breast milk or formula milk. Apart from dietary shortage, VAD could have also been triggered by reduced intestinal absorption of vitamin A. Prolonged deprivation of body requirements for vitamin A leads to vitamin A deficiency disorders (VADDs) that affects gastrointestinal, renal, musco-skeletal organ systems as well as harming growth and development [53]. Xerophthalmia and anaemia are two most common examples of VADDs. In line with vitamin A roles as immunity enhancer, its deficiency is often associated with an increased risk of infections [54, 55]. Respiratory tract infections and diarrhoeal diseases are the most common form of infections with high incidence of mortality along with marked susceptibility to severe measles infection [55–57]. The representation of VADD association to risk of mortality is presented in **Figure 2** below.

4.1.1 Vitamin A deficiency and xerophthalmia

Xerophthalmia refers to a spectrum of ocular manifestations due to VAD and varies according to its severity and age. It is characterised by pathological dryness of the conjunctiva and cornea that turns out as a leading cause of childhood corneal blindness, especially in nutritionally deprived populations [58]. All of such signs encompass those involving impaired retinal sensitivity to light (night blindness) and epithelial disruptions of the cornea and conjunctiva (conjunctival xerosis, Bitot's spot, corneal xerosis and keratomalacia) [59, 60]. The classifications of xerophthalmia stages in order of severity based on WHO criteria are shown in **Table 2** (Section 3.1.1).

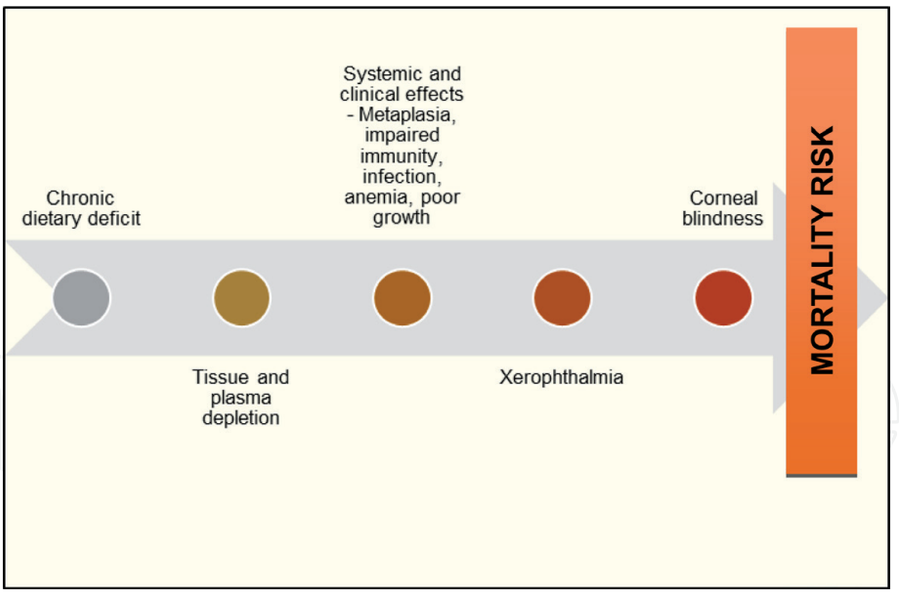

Figure 2.
Representation of VADDs in relation to risk of mortality (adapted from [53]).

Xerophthalmia can occur in any age group with higher possibilities in preschool-age children, adolescents and pregnant women. In line with greater requirements for growth, children are more prone to VAD and xerophthalmia [61]. The initial symptoms of VAD are characterised by impaired adaptation to dark, which starts when the serum retinol concentration falls below 1.0 μmol/L and becomes more often when it falls lower than 0.7 μmol/L. A further drop in serum retinol concentration level below 0.35 μmol/L leads to more frequent and severe xerophthalmia condition [62, 63]. The incidence of xerophthalmia is often associated with higher risk of mortality [57].

Night blindness is generally the earliest manifestation, and it is indicated by vision limitation under dim light and is both a sensitive and specific indicators for low serum retinol levels [63, 64]. Vitamin A in the form of retinal within the eyes combines with opsin to form rhodopsin, which is the photosensitive visual pigment of rods. Rhodopsin level decreases when vitamin A is deficient, and this impairs the rod function causing night blindness [61]. Bitot's spot is the representation of opaque whitish deposits on the scleral conjunctiva, which is the most characteristic sign of problems related to VAD. Conjunctival xerosis is already present at this stage, with the conjunctiva appearing dry and dull. Under conditions where VAD persists, corneal xerosis (hazy cornea) occurs, followed by keratomalacia (liquefaction of part or all cornea) [61].

Several risk factors have been associated with onset of VAD and xerophthalmia based on epidemiological findings. These include demographic, geographic, childhood, parents and household factors. The mechanism of these factor effects on the prevalence of xerophthalmia is summarised in **Table 3**.

4.2 Vitamin A toxicity

On another note, the increase in supply and consumption of fortified foods and supplements led to intake of preformed vitamin A at higher than the recommended level [75]. The side effects of vitamin A excess could occur in two forms, known as hypervitaminosis A and hypercarotenemia [76].

4.2.1 Hypervitaminosis A

Hypervitaminosis A can occur due to both acute and chronic intoxications that generally result from excessive intake of vitamin A from nutritional supplements

Risk factors	Epidemiological findings	References
Demographic	Higher prevalence is observed in neonates, preschool children and pregnant women as they are more vulnerable to be deficient	[57, 65]
Geographic	VAD and xerophthalmia are generally more prevalent in rural areas due to variations of vitamin A-rich food sources, supplementation efforts, limited access and climate changes	[57, 66–68]
Childhood	Breastfed children are at minimal risk of infections and xerophthalmia compared to the non-breastfed children	[57, 69]
Parental	Education literacy is important since it is highly protective against xerophthalmia development and VAD in preschool children	[57, 70]
Household	Poor hygiene, inefficient water supply and cultural and behavioural practices of a family can increase the risk of xerophthalmia. Its prevalence is higher in lower socioeconomic status areas	[57, 70–74]

Table 3.
Risk factors associated with prevalence of VAD and xerophthalmia.

and foods rich in vitamin A [76]. Acute toxicity occurs when adults and children ingest more than their respective recommended dietary allowance within few hours or days, while chronic toxicity results from prolonged consumption of preformed vitamin A over the months or years. However, acute conditions create minimal consequences to human health compared to those under chronic toxicity [77, 78]. Vitamin A, being an essential fat-soluble micronutrient, is quickly absorbed upon ingestion, although it is only cleared slowly from the body. Under such conditions, toxicity could arise either from high-dose exposure or low intake over short or prolonged duration, respectively [79]. Chronic hypervitaminosis A leads to various clinical manifestations that include xerosis, epistaxis, alopecia, weakness and fatigue, bone and joint pain, insomnia, drowsiness, anorexia, bulging fontanelle in infants as well as psychiatric symptoms [76].

Previous research findings have shown that elevated serum concentrations of vitamin A is highly associated with risk of hip fracture [80, 81]. This association is supported by evidence of rat-based experimental studies that demonstrated excessive intake of vitamin A leads to increased bone resorption and less formation at the outer surface that results in bone narrowing [82, 83]. In contrast, the mechanism takes place in opposing effect on the bone marrow surface, where an increase in vitamin A intake reduces bone resorption while increasing its formation. This contradictory effect takes place by the action of vitamin A or its metabolites on osteoblasts at the outer surface together with indirect effect on bone marrow surface [83, 84].

4.2.2 Hypercarotenemia

Hypercarotenemia, which is also referred to as carotenemia or carotenodermia, is a benign phenomenon characterised by pigmentation of the skin. The yellow-orange pigmentation is a result of carotene deposition at the stratum corneum, which is the outermost layer of epidermis [76]. Hyperlipidaemia, consumption of excessive carotene or failure of converting carotenes into vitamin A are conditions that lead to the onset of carotenemia. In view that there is a direct relationship between β-carotene and β-lipoprotein, other medical conditions that are associated with hyperlipidaemia also could lead to this pigmentation. Those conditions include diabetes mellitus, nephrotic syndrome and hypothyroidism. Apart from these, patients suffering from liver disease are also at higher risk of carotenemia due to the

impaired conversion of β-carotene into vitamin A [76]. In contrast to hypervitaminosis A, there are no clear indications of carotenemia to health, and the pigmentation could disappear within weeks to months along with a steady decrease in β-carotene concentration [76, 85].

4.3 Prevention of vitamin A deficiency in nutritionally vulnerable populations

Dietary factors are highly correlated with VAD, especially with increasing requirements at different stages of life. Apart from these, sociocultural factors (intra-household distribution, gender preference) and other economic constraints to achieve adequate dietary requirements for well-being are where a high prevalence of deficiency occurs that leads to prevention efforts. The undertaken prevention efforts should also cater to reduce infectious disease apart from improving vitamin A levels [53]. The prevention approach includes dietary diversification, fortification as well as supplementation. The feasibility of applying each preventive strategy concurrently is somehow dependent on deficiency prevalence and severity as well as infrastructure, financial capacity, potential benefits and safety [86]. In addition, it is also necessary to understand that the success of each preventive programme is interrelated to all levels, inclusive of family, community, district, national and global [53].

4.3.1 Dietary diversification

Dietary diversification refers to efforts of increasing vitamin A intake from commonly accessible and easily available food sources. This approach is deemed feasible provided there is diverse, affordable and continuous supply of vitamin A-enriched dietary sources. Extended breastfeeding is also regarded an important dietary intervention measure, especially as a first-line defence and protection for infants and young children against xerophthalmia. A combined approach of weaning with a routine provision of vitamin A-enriched sources (fruits, vegetables, eggs and others) has proven effective in increasing serum levels of retinols among children [87]. However, under circumstances that the dietary supply is inadequate, home or community gardening will be a good alternative in ensuring food security. In addition to food security, this effort is viable for income generation as well as providing nutritional education to the community. The attempt to involve community-level participation is vital for behavioural adaptation that could considerably improve vitamin A status [53].

4.3.2 Fortification

Fortified foods have been a common intervention globally in combating multiple nutrient deficiencies. The effectiveness of fortification-based intervention is highly dependent on few factors. These include the fortified food vehicle that are widely consumed by high-risk groups, incurs minimal cost and is of a high quality along with centralised processing and distribution [53]. Comparatively, preventive measure via food fortification is much more beneficial and effective than either dietary diversification or vitamin A capsule distribution. Numerous food sources have been subjected to fortification, and these range from oils, flours, cereals, rice, infant formula and also beverages. As such, fortification relates to exploitation of current fortified food consumption patterns towards enhancing vitamin A status [53].

4.3.3 Supplementation

Vitamin A supplementation at high dosage is the most widely practiced prevention measures throughout the world. The supplementation is channelled on

an interval basis with a designated duration. This mode of prevention comprises community involvement and efforts to provide vitamin A supplements to nutritionally vulnerable groups, especially preschool children and mothers. The rationale for high-dose supplementation of vitamin A is based on the assumption that this fat-soluble compound will be stored in the liver and is released together with the transport proteins as per body tissue requirement [53].

5. Conclusion

Vitamin A is one of the fat-soluble vitamins that are vital for various biological roles in the human body, as it is essential for embryogenesis up to adulthood. It can be sourced from both animal-based (preformed vitamin A) and plant-based (provitamin A) foods. The evaluation of whether a population is vitamin A deficient or excess is determined by status monitoring. Biological and biochemical indicators are the most widely applied parameters in assessment of vitamin A status. Vitamin A deficiency or toxicity state arises under conditions where the dietary intake does not comply with recommended levels. It is crucial to note that both conditions could lead to various health complications with VAD leading to mainly xerophthalmia, increased infection risk and anaemia, while toxicity could result in chronic hypervitaminosis and hypercarotenemia. In line with this, prevention efforts that could improve vitamin A status are widely explored. Dietary diversification, fortification and supplementation are the three main approaches that are widely applied for this purpose. These continuous efforts are believed to be able in improving vitamin A status among the vitamin A-deficient populations.

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Conflict of interest

It is declared that there is no conflict of interest involved in the publication of this book chapter.

Abbreviations

apo-RBP	apo-retinol-binding protein
CIC	conjunctival impression cytology
CRBP	cellular retinol-binding protein
DR	3, 4-didehydroretinol
DRA	3, 4-didehydroretinyl acetate
Holo-RBP-retinol complex	holo-retinol/retinol-binding protein complex
HPLC	high-performance liquid chromatography
ICT	impression cytology with transfer
ID	isotope dilution
LRAT	lecithin: retinol acyltransferase

MRDR	modified relative dose response
RA	retinoic acid
RAE	retinol activity equivalent
RAR	retinoic acid receptor
RBP	retinol-binding protein
RDR	relative dose response
RE	retinol equivalent
ROS	reactive oxygen species
RXR	retinoic X receptor
VAD	vitamin A deficiency
VADDs	vitamin A deficiency disorders
XF	xerophthalmia fundus
XN	night blindness
XS	corneal scars
X1A	conjunctival xerosis
X1B	Bitot's spots with conjunctival xerosis
X2	corneal xerosis
X3A	corneal ulceration with xerosis
X3B	keratomalacia

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