REVIEW ARTICLE

Vitamin A deficiency and xerophthalmia

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Abstract

Objective: to review cases of vitamin A deficiency and the effects of vitamin A supplementation on child morbidity and mortality.

Methods: articles published in scientific journals, technical and scientific books, and also publications by international organizations were used as source of information.

Results: clinical manifestations of xerophthalmia affect the retina (night blindness), the conjunctiva (conjunctival xerosis, with or without Bitot spots), and the cornea (corneal xerosis). Corneal xerosis may lead to corneal ulceration and liquefactive necrosis (keratomalacia). A priori, these signs and symptoms are the best indicators of vitamin A deficiency; they are, however, extremely rare. Laboratory indicators include Conjunctival Impression Cytology and serum retinol concentrations. The World Health Organization (WHO) recommends the use of two biological markers in order to characterize vitamin A deficiency in a given population. If only one biological marker is used, this marker has to be backed up by a set of at least four additional risk factors. Corneal xerophthalmia should be treated as a medical emergency; In the event of suspected vitamin A deficiency, a 200,000 IU vitamin A dose should be administered orally, repeating the dose after 24 hours (half the dose for infants younger than one year). Vitamin A supplementation in endemic areas may cause a 23 to 30% reduction in the mortality rate of children aged between 6 months and five years, and attenuate the severity of diarrhea. The methods for the control of vitamin A deficiency are available in the short (supplementation with megadoses), medium (food fortification), and long run (diet diversification).

Conclusion: there is evidence of vitamin A deficiency among Brazilian children. Pediatricians must be aware of the signs and symptoms of this disease, however sporadic they might be. It is of paramount importance that vitamin A be included in public policy plans so that we can ensure the survival of children.


Background

The expression vitamin A deficiency is used to describe states of subclinical deficiency of vitamin A, while xerophthalmia designates the group of ocular signs and symptoms related to this deficiency. Night blindness was first described in Egypt around 1500 BC; the oldest medical paper known in the Western world, called Eber’s papyrus (1600 BC), stated that people affected by day blindness should follow a diet high in liver - a prescription that had also been recommended by Hippocrates. However, a detailed description of corneal lesions and the possible nutritional origin of xerophthalmia were registered for the first time in the medical literature by Brazilian physician Manuel da Gama Lobo, who, in 1864, described typical ocular lesions in slave children in Rio de Janeiro. According to Gama Lobo, the occurrence of this ocular syndrome may be related to nutritional inadequacy; at that time he foresaw the existence of vitamins by asserting: this type of ophthalmia results from the lack of convenient and sufficient nutrition. 

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Yet the discovery and isolation of vitamin A only occurred very recently. In 1913, professor Elmer McCollum and his colleague Marguerite Davis discovered a fat-soluble factor in butter and egg yolk that was absolutely necessary for the growth of mice. Later on, this substance was identified as the healing factor for nutritional blindness and received the name of vitamin A.3

Vitamin A deficiency and xerophthalma in Brazil

After Gama Lobo’s first findings, there were a series of vitamin A and xerophthalma case reports in Brazil. In 1883, Hilario de Gouveia, professor at the School of Medicine (Rio de Janeiro), observed the existence of night blindness in undernourished slaves.4 After slavery was abolished in Brazil, fewer cases were reported, except in times of acute food shortage such as prolonged droughts in semiarid regions. Euclydes da Cunha in “Os Sertões”, originally published in 1902, described day blindness as the false blindness that usually occurred during dry periods.5 Robalinho Cavalcanti registered the occurrence of day blindness during the 1932-33 drought6 and Josue de Castro, in 1946, described “day blindness and other vitamin deficiencies, common in the region of Sertões during calamitous droughts” in his book The Geography of Hunger.7 In 1951-52, data obtained from the Department of Ophthalmology at Fortaleza Health Center, State of Ceará, showed a high prevalence of xerophthalma, requiring compulsory administration of vitamin A to all pediatric patients.8

In the last decades, evidences of vitamin A deficiency and xerophthalma have been gathered especially in northeastern, and sporadically in northern and southern Brazil. 64 children with corneal xerophthalma were followed up between 1963 and 1965 in the city of Florianópolis; 80% of these children had ingested nonfortified skimmed milk, donated by the International Foundation for Children’s Care, known today as the United Nations Children’s Fund (UNICEF).9

The epidemiology of vitamin A deficiency in northeastern Brazil has been recently reviewed10. A clinical nutritional study comprising three bioclimatic regions of the State of Paraíba, conducted in 1981-2, showed a significant increase in the prevalence of Bitot spots and corneal scars in the middle region of Sertões, especially in the intermediate harvest periods.11 Clinical manifestations of moderate xerophthalma, as well as cicatricial sequelae, were also observed in the State of Paraíba in children aged between 2 and 28 months in the subsequent years, mainly during the prolonged drought that lasted from 1981 to 1984.12 In 1982, the University Hospital of João Pessoa implemented a system to actively search cases of xerophthalma and, as a result, several cases of ocular lesions, especially those with involvement of the cornea, were diagnosed and followed up.13 In 1986, clinical evidence of moderate xerophthalma was also observed in the state of Rio Grande do Norte.14 Biochemical data obtained in Fortaleza, and in other towns in the state of Ceará, and also in Recife between 1987 and 1991, showed an inadequately high concentration of serum retinol.15 Inadequately high concentrations of serum retinol and low consumption of foods rich in vitamin A were also reported in suburban areas of the semiarid regions of Bahia in 1989.16

Physiopathology
Absorption, storage and transport

There are two vitamin A food sources: preformed vitamin A (retinyl esters), of animal origin, and provitamin A (carotenoids), of vegetal origin.17 The expression provitamin A comprises nearly 50 compounds with biologically active vitamins, among which all-trans-beta-carotene is the most important.

In the stomach, retinyl esters and other carotenoids are subjected to the action of proteolytic enzymes, are separated from the food and are aggregated into globles together with other lipids. In the intestine, retinyl esters are hydrolyzed by enzymes found in enterocytes, are incorporated into the micelles which are formed through biliary secretions, and finally absorbed.18 In physiological amounts, retinol is more efficiently absorbed than carotenoids; retinol absorption is approximately 70-90%, while the absorption of carotenoids is only 20-50%.19 By increasing the intake of these substances, we still have a highly efficient retinol absorption (60-80%) in sharp contrast to a plummeting carotenoid absorption of less than 10%.20

Several factors influence the absorption of vitamin compounds, including intestinal parasite infections such as giardiasis, ascariasis and strongyloidiasis21 in patients with a high parasite count.22 In northern Brazil, the treatment of intestinal parasite infections (ascariasis and giardiasis) increased retinol levels after supplementation; therefore, given the endemic nature of parasite infections in this region, antiparasitic therapy should precede the distribution of any food and/or supplement.23 In India, however, antiparasitic therapy did not increase the beneficial effects of vitamin A megadoses.24 The same authors25 found a reduction in vitamin A absorption in children with acute diarrhea, in comparison to healthy children; yet, despite malabsorption, almost 70% of the 100,000 IU (International Units) megadose, diluted in an oral rehydration solution, was absorbed. Patients with intestinal resections have a poor rate of absorption and pancreatic diseases reduce the absorption of fat-soluble preparations.26 Some authors warn about the fact that subjacent nosological status such as cystic fibrosis can lead to vitamin A malabsorption.27
Dietary fat content should also be considered as far as vitamin A absorption is concerned. The restriction on carotenoid absorption is extremely important in young children, whose diet consists of foods that contain little fat. These data evoke justified concern as vitamin A sources, in most countries with endemic deficiency problems, basically consist of carotenoids instead of preformed vitamin A.28

Almost all the absorbed retinol is stored in parenchymal liver cells, corresponding to approximately 90% of the total body stores of vitamin A.29 The remaining 10% are distributed among blood cells, bone marrow, adipose tissue and spleen. Retinol circulates from the liver to peripheral tissues through a retinol-binding protein (RBP), with molecular weight of 21,000, and a retinoid-binding site.30 After binding to membrane receptors, retinol enters the target cell and the RBP is again released into bloodstream; RBP is later degraded or recycled.

**Physiological role**

Vitamin A is essential for the maintenance of normal physiological functions, with a wide (yet partially known) scope of action that includes functions related to visual cycle, integrity of biological membranes, epithelial maintenance and differentiation, glucoprotein formation, production of mucus, and protection against infections, which is mediated by immunoresponse modulating action.

The role of vitamin A in the visual cycle, ocular membranes and production of mucus will be presented in more detail when the ocular signs and symptoms of xerophthalmia are described. However, the key role of vitamin A in maintaining ocular integrity should be emphasized, since ocular lesions that originate from its deficiency are the main cause of preventable blindness in children. The World Health Organization (WHO) estimated that xerophthalmia affected nearly 3 million children around the world in 1995.31

The role of vitamin A as immunoresponse modulator has been confirmed by several in vivo and in vitro experiments;32-34 however, their conclusions require careful interpretation. In general, we may affirm that vitamin A increases humoral immune response, the concentration of active antibodies, the number of splenic antibody-producing cells, and local immunity, in addition to stimulating phagocytosis and the activity of polymorphonuclear neutrophils and macrophages.33

**Signs and symptoms of xerophthalmia**

When liver vitamin A stores are too low or nonexistent, individuals are at potential risk of suffering from the effects of its deficiency. Low vitamin A intake, absorption disorders or an increase in metabolic demand can accelerate the appearance of typical ocular manifestations inherent to xerophthalmia.18

The main clinical manifestations of vitamin A deficiency in the ocular system chiefly occur in three ocular structures: retina, conjunctiva and cornea (Table 1).

The involvement of the retina occurs due to biochemical/functional changes - night blindness - and also structural changes - fundus xerophthalmicus. Although this type of involvement has marginal significance, it has proved to be an indicator of vitamin A deficiency as sensitive and specific as the signs presented by the anterior segment of the eyeball.35

In the visual cycle, retinal (an oxidized form of retinol) is bound to specific proteins (opsins) to form rod and cone visual pigments in the retina. In the intracellular membranes of rods - cells functionally responsible for scotopic vision - we find rhodopsin, which is formed by the retinal + opsin complex. The photochemical reactions of vision are triggered when the retina is reached by light stimulus. In the presence of light, 11-cis retinal is turned into all-trans-retinal. These alterations change the geometric configuration of retinal and are followed by a global change in the rhodopsin molecule, which works as a molecular trigger, producing a stimulus in the nerve terminals of the optic nerve; the stimulus is therefore transmitted to the brain. 11-cis-retinal is used as a chromophore to the cones, which are essential for photopic and color vision; actually, the rhodopsin found in rods is the one intrinsically responsible for night vision.36

If vitamin A supplementation is too low, night blindness will be one of the first symptoms of xerophthalmia since rhodopsin requires high concentrations of 11-cis-retinal to create a highly sensitive visual film.37

Sommer et al, in their studies in Indonesia,38 concluded that the history of night blindness is a reliable method for the diagnosis of xerophthalmia. The word or expression used by mothers to describe the loss of night vision is an important tool to diagnose the extension of the problem. However, the authors insist that it is important to know the correct local expression in order to research about the phenomenon. The use of night blindness history as a diagnostic method in population studies is also restricted by the unavailability of reliable data gathered from very young children, who are at higher risk for nutritional blindness.12-18

Other ocular manifestations, which are not related to vitamin A deficiency, cause loss of scotopic vision. The most frequent manifestations include high myopia, glaucoma with great visual field disorders, optic atrophies and several pathologies that involve the retinal tapetum (e.g.: retinosis pigmentii).

The keratinizing metaplasia of the conjunctival epithelium, with the disappearance of mucin-producing cells and consequent tear film instability, cause conjunctival xerosis, in which the conjunctival surface presents brightness and transparency loss, going through a hardening and thickening process. Due to the subjective nature of clinical
Signs, conjunctival xerosis, as an isolated criterion, is not suitable for the diagnosis of xerophthalmia. This occurs because the ocular conjunctiva is frequently affected by other morphological changes that could remarkably reduce the power of discrimination of clinical signs in the diagnosis of xerophthalmia. Conjunctival alterations, especially concerning palpebral fissure, are often attributed to factors typically found in tropical countries such as environmental and racial characteristics. The most commonly described manifestations include thickening of the conjunctiva, pingueculae, pterygia, perilimbal pigmentation areas, conjunctival and episcleral melanosis. On the other hand, well-defined nosological entities such as the dry eye syndrome, trachoma and ocular pemphigoid should be considered in the differential diagnosis of xerophthalmia.

There is formation of Bitot spots in the areas of the conjunctiva where xerosis is more intense. These spots are depositions of spumous or caseous material that result from the accumulation of desquamated epithelial cells, meibomian gland phospholipids and saprophytic microorganisms (Corynebacterium xerosis). These lesions are asymptomatic and easily removable, except in some caseous cases that present pronounced adherence to the conjunctiva; they are oval or triangular, condensed or scattered, usually adjacent to the corneoscleral limbus, in the temporal and nasal regions of the bulbar conjunctiva, corresponding to the interpalpebral fissure. Nasal Bitot spots, although less perceptible, suggest a narrower relationship with vitamin A deficiency. The specificity of Bitot spots, as a clinical sign of vitamin A deficiency, has been questioned, since the spots observed in adults and school-age children are usually adherent and persistent after treatment and may indicate sequelae of previous xerophthalmia. Therefore, Bitot spots should be associated with night blindness in order to maximize clinical sign reliability in the diagnosis of xerophthalmia.

The decline in the production of the mucus that interfaces the aqueous component of the precorneal tear film with the hydrophobic surface of the cornea, resulting in early tear film rupture, gives the cornea a rough, dry, wrinkled and brightless aspect, expressed by the clinical sign of corneal xerosis. The keratinized epithelium is extremely vulnerable, and the lower corneal region, which is more exposed and unprotected, may undergo an erosive process, causing the destruction of the corneal epithelium, and the exposure of Bowman's layer. The stage of corneal erosion, combined with intense photophobia, is the clinical border where all subjacent corneal lesions present opacity as cicatricial sequela.

The involvement of Bowman's membrane and subjacent stroma is the most severe lesion caused by xerophthalmia. A usually single corneal ulcer, round or oval in shape, with clearly defined edges, is initially formed. The rupture of the anatomical barrier integrity caused by ulceration favors the release of proteolytic enzymes. These enzymes produce liquefactive necrosis of the corneal stroma, which characterizes keratomalacia.
Despite severe ocular involvement, the eye remains undisturbed, hyporeactive, with no significant inflammatory signs, except in the presence of concomitant secondary infection. In a randomized clinical assay, showed that the frequent use of antibiotic therapy failed during corneal scarring; daily practice has shown us that only a treatment with vitamin A can reverse cases of xerophthalmia.

If corneal involvement is restricted to xerosis, the ocular surface is totally rehabilitated (without sequelae) after specific vitamin treatment. If the lesion affects Bowman’s membrane and/or the subjacent stroma, corneal opacity of variable intensity (nebula, macula or leukemia), appears as a sequela, depending on the intensity of the process. In cases of ulcer or keratomalacia, the cicatricial lesion that results from corneal stroma loss is called descemetocoele. If the cornea is perforated, with loss of ocular contents, there is atrophy of the eye (phthisis bulbi). In other cases, in which the anterior chamber is partially restored after perforation, we have adherent leukoma. On the other hand, the development of staphyloma is established if the anterior chamber is obliterated by iridocorneal synchiae, with consequent increase in intraocular pressure, due to the partial destruction of the cornea.

It is important to consider that corneal involvement may precede retinal and conjunctival involvement, especially in underfed and seriously ill infants.

Epidemiological markers

Clinical signs

A priori, the clinical ocular signs and symptoms of vitamin A deficiency are the most reliable indicators for its diagnosis. However, we should be aware that some clinical manifestations are not specifically related to vitamin deficiency; in addition, there is still some difficulty in evaluating and standardizing these indicators.

The diagnosis of night blindness has been primarily based on reports made by children’s mothers or guardians, as previously stated. However, a more objective procedure has been proposed to assess this functional alteration: a quick test to estimate the dark adaptation curve. The results of adaptometry, compared to serum retinol levels, have been controversial. Some authors found a sensitivity of 95% and a specificity of 91%, while others did not find any correlation between these parameters.

The identification of conjunctival xerosis is extremely subjective; therefore, it is not possible to use it as an isolated clinical sign of xerophthalmia. The importance of early diagnosing xerophthalmia stimulated the use of vital staining (Lissamine green and rose bengal) to better characterize cases of xerophthalmia; nevertheless, results were not conclusive. Bitot spots and the signs of corneal involvement have to be exclusively diagnosed through clinical examination, and reinforced by therapeutic testing.

According to WHO guidelines, xerophthalmia may be regarded as a public health problem when the prevalence rates of night blindness and Bitot spots in infants aged between 6 and 71 months exceed, respectively, 1.0% and 0.5%. The critical prevalence rates for active corneal involvement and cicatricial sequelae are respectively 0.01% and 0.05% (Table 1).

Conjunctival Impression Cytology (CIC) is the technique used to remove superficial layers of the ocular conjunctiva using a cellulose acetate filter paper for subsequent histological analysis. Most authors have used the presence/absence of goblet cells as a preponderant criterion for cytological diagnosis, in an attempt to minimize false positive results. However, animal studies suggest that corneal keratinization precedes the loss of goblet cells; hence, some researchers emphasize that it is important to include information about goblet cells and on the morphology of epithelial cells in the diagnostic criteria, thus enhancing the sensitivity of the cytological method.

The interpretation of cytological test results has shown a high level of interobserver and intraobserver reproducibility. Conjunctival impression cytology is inexpensive and painless, eliminating the use of topical anesthetics, which could work as artifacts in the microscopic interpretation of the samples. This technique may be used in the field, with a satisfactory level of adherence. Major limitations include the impossibility of use on children younger than 3 years, and the interference of environmental factors such as excessive humidity and high temperatures, which may affect filter paper properties or the transfer technique.

According to WHO guidelines, the prevalence of abnormal conjunctival cytology below 20% is considered a mild public health problem; prevalence rates above 20% and below 40% characterize a moderate public health concern; and prevalence rates above 40% are regarded as a serious public health problem.

Biochemical markers

Hepatic retinol: liver vitamin A concentrations may be used to estimate the levels of vitamin A, since 90% of the total body stores of vitamin A are found in the liver. However, liver biopsy, in the absence of pathology, is not ethically justifiable. According to Underwood, this methodology is only used in diagnostic or postmortem cases. Nevertheless, it is possible to estimate liver vitamin...
A stores indirectly. Inadequate nutritional supplementation leads to the depletion of liver vitamin stores, with consequent decrease in the release rate of vitamin A. The synthesis of RBP continues, resulting in the accumulation of preformed carrier protein (APO-RBP). Exogenous administration of vitamin A triggers the release of HOLO-RBP, in time and concentrations proportional to the amount of preformed carrier in the liver. The Relative Dose Response (RDR) test follows this principle. After collecting a fasting blood sample for retinol dosage (vitamin A in time 0 = vitA0) a solution of retinyl palmitate (450-1000mg) is administered orally and, 5 hours later, a new blood sample is collected in order to evaluate postsupplementation retinol level (vitA5). The RDR is calculated through the following formula:

\[
\text{RDR} = (\text{vitA5} - \text{vitA0} \times 100 / \text{vitA5})
\]

If the RDR is >20%, the response is positive, indicating inadequate liver vitamin A store. RDR values above 20% in inpatients were correlated with hepatic retinol concentrations below 0.70mmol/l (20µg/dl). Another study revealed a high test specificity in individuals with adequate intake and normal liver stores of vitamin A.

Although this test can be used in the field, the need for two phlebotomies is a limiting factor for its large-scale application. On the other hand, test results may be influenced by infections and possibly by protein adequacy and liver diseases, where RBP concentrations are too low, not responding to the test. However, mild or moderate protein-energy malnutrition seemingly does not interfere with test results.

The RDR test has been recently changed. In this new procedure (MRDR), retinol palmitate is replaced with 3,4-didehydroretinol (DR), a natural and biologically active compound of vitamin A that is bound to RBP without altering retinol (R) concentrations. Only one blood sample is collected 5 hours after the oral administration of 3,4-didehydroretinol. The downside of the MRDR test is that it is not commercially available. Similarly to the RDR test, the MRDR may also be affected by infections or other common childhood diseases in developing countries, since RBP concentration is reduced in the acute phase of infection.

The RDR and MRDR tests have been used as risk indicators. A prevalence rate of vitamin A deficiency below 20% in children aged between 6 and 71 months indicates a mild public health problem; prevalence rates between 20% and 30% characterize a moderate public health concern; and prevalence rates above 30% are regarded as a serious public health problem.

\[\text{Serum retinol}:\] the dosage of serum retinol has been the most frequently used biochemical test for the diagnosis of vitamin A deficiency. Although the use of this technique is widespread, it is reliable only when vitamin A concentrations are excessive or too low. Therefore serum retinol concentrations in other biochemical tests do not show a good correlation with the RDR test or liver biopsy results.

Traditionally, serum retinol concentrations below 20µg/dl (0.70µmol/l) are considered low, and values below 10 µg/dl (0.35 µmol/l) are insufficient. The prevalence of low serum levels (between 2% and 10%) in children aged between 6 and 71 months characterizes a mild public health concern; prevalence rates between 10% and 20% indicate a moderate public health problem; and prevalence rates above 20% are regarded as a serious public health problem.

\[\text{Retinol in breastmilk}:\] concentrations of vitamin A in breastmilk have been a reliable indicator of vitamin A status in a given population. These concentrations help outline the areas at greater risk, and are among the best indicators to evaluate whether or not an intervention is efficient. Concentrations equal to or below 30µg/dl (1.05 µmol/l) indicate vitamin A deficiency. A prevalence rate with inadequate levels below 10% characterizes a mild public health problem; prevalence rates equal to or below 25% indicate a moderate public health concern; and prevalence rates above 25% characterize a serious public health problem.

\[\text{Other markers}:\] New markers and also some markers still under development have been proposed to evaluate vitamin A status. Among new approaches, the isotope dilution method, according to Underwood, is the best marker, since it measures the total body store of vitamin A. The method is based on the principle that a new labeled vitamin A uniformly combines with the body store of vitamin A. The dilution of this labeled vitamin A in blood, considering the administered amount, is used to calculate the total amount of vitamin A, assuming that a constant amount of vitamin A is found in the liver. This is the only method that measures the relative status of vitamin A directly and quantitatively. Since this method requires the use of costly isotopes and sophisticated equipment, it is not widely used on humans.
Although the inquiry into the consumption of vitamin A sources is inexpensive and easily conducted in the field, its precision has been harshly criticized. Theoretically, nutritional history may be a reliable indicator of vitamin A status, considering that it is obtained at least semiquantitatively, representing the usual standard of food consumption throughout a given time period, and assuming that the amount of vitamin A required by each individual and population at large is well-known. The difficulty in obtaining quantitative information on vitamin A intake has been well documented in populations where the sources of food are variable. Nevertheless, a semiquantitative analysis, based on the frequency of consumption, may be used to categorize groups at risk for inadequate vitamin A status. The International Vitamin A Consultative Group (IVACG) has elaborated a guide to help categorize children in developing countries, where 80-90% of food consumption consists of carotenoids found in limited food groups. This guide is based on a food composition table adapted to locally available foods. However, some authors warn against the difficulty in analyzing and interpreting the nutritional data, considering that food composition tables are inappropriate or outdated in several countries.

Using the consumption marker, a region or population is considered to be at potential risk for vitamin A deficiency when the consumption of vitamin A-rich foods at least three times a week occurs in less than 75% of homes or vulnerable groups.

Vitamin A status is a continuum that ranges from clinical deficiency to toxicity. So far, no single method has been able to satisfactorily identify the transitional states (marginal, adequate, excessive) that form the spectrum of vitamin A status. The combination of several methods is certainly more reliable when assessing vitamin A status. The most recent guidelines recommend the use of at least two biological markers to characterize vitamin A deficiency. If only one biological marker is used, this marker has to be backed up by a set of at least four additional risk factors, comprising nutritional, demographic, ecological and social and sanitary aspects, such as:

- <50% of infants younger than 6 months submitted to exclusive breastfeeding
- ≥30% of infants aged between 0 and 3 years with height deficiency (<-2 standard deviations of the reference population from the National Center for Health Statistics, NCHS)
- ≥15% of infants with low birth weight (<2.5kg)
- >75/1000 of childhood mortality rate
- >100/1000 of mortality rate in childhood (ages 1-4 years)
- <50% of children with complete vaccination coverage
- >1% of deaths from measles
- >50% of mothers with no formal education
- <50% of homes with treated water

**Treatment and prevention**

**Clinical treatment of active forms**

The clinical evidence of vitamin A deficiency should be treated as a medical emergency, especially if there is corneal involvement. In the event of suspected vitamin A deficiency, the standard therapeutic method should be immediately applied. A dose of 200,000 IU of vitamin A (110mg of retinol palmitate or 69mg of retinol acetate) is recommended at the moment of diagnosis and another dose 24 hours later. A third dose, whenever possible, should be administered after 4 weeks. Half the dose should be administered to infants younger than 1 year or weighing less than 8 kg. In the case of women at reproductive age, the daily dose should not exceed 10,000 IU due to the potential teratogenic risk posed by an excessive dosage.

Vitamin A absorption is significantly higher in water-soluble preparations, and oral administration is more practical and as effective as the parenteral route in the treatment of severe xerophthalmia.

When vitamin A deficiency and protein-energy malnutrition coexist, vitamin A should be added to the nutritional rehabilitation therapy to avoid the precipitation of xerophthalmia; in these cases, the anabolic activity is reactivated, vitamin A requirement is suddenly increased, and the depleting stores are rapidly used.

**Preventive treatment**

Vitamin A, mortality and diarrhea in childhood: The impact of vitamin A supplementation on the mortality of children aged between 6 months and 5 years mortality has aroused the interest of the scientific community in the last few years. Eight randomized intervention placebo controlled assays, employing adequate methodology and sample size, were carried out in Asian and African countries. Six of these assays presented a significant reduction in the total mortality rate in children who received vitamin A supplementation (between 19% and 54%); in the other two assays, no effect was found. Three independent metanalyses using the data obtained through these intervention studies were performed, two of which were conducted by researchers who were not directly or indirectly involved in the original studies. The results of the metanalyses showed an average reduction of 23% and 30% in mortality.

The prevalence of some baseline markers, such as xerophthalmia, weight and height deficiency, and mortality in the control group (used as a baseline mortality proxy) neither predicted the final result nor defined the situations in which vitamin A supplementation would be most beneficial. Similarly, the different periodicity of supplementation in the six assays that yielded positive results seemed to be equally effective: 2 assays used...
megadoses every 6 months, 2 of them used megadoses every 4 months, another one administered small weekly doses and the last assay employed a condiment fortified with vitamin A (monosodium glutamate), which resulted in small daily doses. The possibility of a pharmacological (and not physiological) effect due to a vitamin megadose may be safely discarded to some extent. The data obtained from five out of the six assays that showed an effect on mortality could be aggregated for metaanalysis, as far as deaths resulting from specific causes were concerned. The only significant effect on specific mortality was a 32% reduction in deaths caused by diarrhea in children who received supplementation, that is, a relative risk (RR) of 0.68 and a 95% confidence interval (95%CI) between 0.57 and 0.80. However, it necessary that results be carefully interpreted since the cause of death, in most studies, was informed by family members in their anamnesis (“verbal autopsy”).

Several studies were carried out to analyze the effect of vitamin A supplementation on the morbidity of children, especially due to diarrhea and acute respiratory infection. The effect on the prevention of diarrhea is little or negligible. Only one study on morbidity, which was well-delineated and had an adequate sample size, showed a little yet significant 6.0% reduction in the incidence of diarrhea (RR=0.94 and 95%CI=0.90 - 0.98). In the other four studies, no effects on the average daily prevalence or incidence of diarrhea were registered. Only one study, in which the discontinuation of patient follow-up may have interfered with the analysis, showed different and intriguing results: a slight (significant) increase in the incidence of diarrhea and acute respiratory infection.

However, the evident effects of vitamin A are enhanced in cases of severe diarrhea. In one intervention study, vitamin A supplementation accounted for a 9% reduction in the incidence of moderate diarrhea (RR=0.91 and 95%CI=0.85 - 0.98) and for a 20% reduction in severe diarrhea (RR=0.80 and 95%CI=0.65 - 0.98). Diarrhea episodes that lasted for 3 or more days, with 4 or fewer liquid or semisolid stools within 24h, were considered moderate; those that lasted 3 or more days, with 5 or more liquid or semisolid stools within 24h were regarded as severe. In the same study, the average daily prevalence of diarrhea was reduced since definition included only the most severe episodes, with ≥4, ≥5, and ≥6 liquid or semisolid stools within 24h.; the prevalence rates among children who received vitamin A supplementation and those who were given placebo were respectively 0.90 (P=0.049), 0.80 (P=0.005) and 0.77 (P=0.006). Another assay showed a 36% reduction in the average daily prevalence of diarrhea associated with fever (infants older than 23 months). In a more comprehensive assay, the group that received vitamin A supplementation presented 15% fewer signs and symptoms of dehydration than the placebo-controlled group (RR=0.85 P<0.001), 12% demanded less medical care (RR=0.88 P<0.02), and 38% showed a reduction in hospitalization rates (RR=0.62 P<0.02).

**Preventive treatment measures**

Several universally accepted methods for the control and eradication of micronutrient deficiencies are available in the short, medium and long run. However, up to now, most programs in risk areas have opted for the massive administration of vitamin A. In Brazil, vitamin A supplementation started to be implemented in 1983 by the National Program on Immunization in the northeastern states and, on a smaller scale, by local health systems, at outpatient clinics. In addition to universal distribution (children between 6 months and not yet 5 years), the distribution of the population into specific groups (children with acute and/or prolonged diarrhea, measles, severe malnutrition and pregnant women in the immediate postpartum period) has been recommended.

The periodical administration of vitamin A is physiologically aimed at maximizing liver vitamin stores through a vitamin A megadose. In theory, this supplementary dose of vitamin A would adequately protect the body against vitamin A deficiency for a 6-month period. The protective effect is likely to vary in different contexts due to some factors that interfere with vitamin A bioavailability. Some studies showed that the administration of a vitamin A megadose every six months was able to guarantee an adequate vitamin A status. This status was measured by the Relative Dose-Response test (RDR) for a period of just four months. The toxic risks of universal vitamin A administration have been one of the major reasons for resisting this kind of intervention. Symptoms such as nausea, vomiting and occasional bulging fontanelle have been described; nevertheless, these side effects disappear without any specific treatment within one or two days after vitamin A supplementation. A recent study carried out in Brazil attempted to identify the occurrence and nature of possible acute adverse effects caused by vitamin A megadose supplementation (100,000 and 200,000 IU), supplied together with mass immunization. A sample of 852 children aged between 6 and 59 months were followed up 24 hours before and 72 hours after vaccination, and categorized into two groups: 416 who received vitamin A together with the vaccines, and 436 who received the vaccines but did not receive vitamin A (control group). 24 hours prior to vaccination, children in both groups had a similar frequency of diarrhea, vomiting and fever; however, anorexia was more prevalent in the group that received vitamin A and persisted throughout the follow-up period. Results suggest that no adverse effects, especially diarrhea, vomiting, fever or anorexia were associated with vitamin A intake combined with mass vaccination, especially Sabin, DPT and antimeasles vaccines.
Experiments with food fortification yielded thriving results in Asia\textsuperscript{58} and in Central America.\textsuperscript{79} However, the large-scale adoption of these measures, due to multiple factors that restrict their implementation, should be carefully analyzed, given the peculiarities of each region or country.

Large-scale interventions targeted on increasing the availability and consumption of vitamin A food sources are practically nonexistent; the implementation of such measures should consider economic, social, educational and cultural factors.\textsuperscript{28} Foods rich in preformed vitamin A are expensive, thus restricting their regular consumption by the risk population. Fruit and vegetables are important sources of beta-carotene, and are more accessible to low-income populations, although the typical eating habits of each region impose restrictions on the consumption of certain products, especially vegetables.\textsuperscript{10} The promotion of a large-scale consumption of beta-carotene would be the most appropriate way to approach the matter. Beta-carotene has an advantage over retinol in terms of toxicity, availability and cost-benefit; it may be administered to pregnant women to increase their body stores and concentrations of vitamins in milk, being safer than retinol and presenting no confirmed teratogenic risks.\textsuperscript{80} Until now, there have been no reports showing toxicity related to excessive intake of beta-carotene; hypercarotenemia only causes a yellowish deposit on the skin.

In India, children with xerophthalmia were treated in a nutrition rehabilitation center, through the intake of local foods containing proteins and beta-carotene. This nutritional treatment associated with general medical treatment was enough to reverse the cases of conjunctival and corneal xerosis.\textsuperscript{81} In Brazil, the consumption of buriti palm fruit (\textit{Mauritia vinifera mart}) - a rich source of carotenoids - using a daily administration of 134mg of retinol equivalent during 15 days, managed to reverse the clinical and biochemical evidences of vitamin A deficiency.\textsuperscript{14} However, studies conducted in Indonesia failed to show an increase in vitamin A status after an increased consumption of green and/or yellow leaves; On the other hand, serum retinol levels substantially increased when purified beta-carotene was administered through a formula.\textsuperscript{82}

**Prognosis**

Clinical practice has revealed that treatments with vitamin A reverse cases of xerophthalmia; however, the scars in ulcerated areas are not removed.\textsuperscript{12,13,38,40}

Extremely high mortality rates of children with xerophthalmia during hospital stay are quite remarkable.\textsuperscript{40,83} Unfortunately, these mortality rates are still high even after children are discharged from hospital. Approximately two thirds of children with partial or total blindness due to xerophthalmia died some months after the onset of visual deficiency.\textsuperscript{84,85} Among the several factors that may contribute to these high mortality rates we find social and family rejection of visually-impaired individuals, nutritional disorders and their consequences that originate from the greater difficulty and increased risks for accidents these individuals have to cope with in order to feed and protect themselves.\textsuperscript{85}

**Conclusions**

There is evidence of vitamin A deficiency among Brazilian children, especially in poverty-stricken communities in the semiarid northeastern region.\textsuperscript{10-16,30} Pediatricians must be aware of the signs and symptoms of this disease,\textsuperscript{13} however sporadic they might be, in addition to the associated risk factors.\textsuperscript{31} In view of the results, which show a significant reduction in mortality and severity of morbidity in childhood, it is of paramount importance that vitamin A be included in public policy plans so that we can ensure the survival of children.

**References**


