Vitamin A deficiency and its role in infection

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Vitamin A is essential for vision, growth and reproduction, and is involved in the control and differentiation of epithelial tissues (ZILE & CULLUM, 1983), and it is undoubtedly this last function together with a role in immunoprotection which links vitamin A status most closely with infection. The supply of adequate dietary vitamin A is an enormous problem in many parts of the Third World and pre-school children are particularly at risk. The earliest clinical sign of vitamin A deficiency is impaired vision in dim light, ‘night blindness’, but even at this stage vitamin A reserves are already dangerously low and this xerophthalmia can progress, as epithelial integrity fails and supplies remain inadequate, to corneal xerosis, ulceration, blindness and often death (DARNTON-HILL, 1988). The recent large case-control studies in Indonesia have also emphasized the considerable public health importance of mild xerophthalmia (‘night blindness’ and Bitot’s spots), which is associated with both increased mortality (SOMMER et al., 1983) and morbidity from respiratory and diarrhoeal diseases (SOMMER et al., 1984; MILTON et al., 1987). Furthermore, supplementation with retinol of children in areas were xerophthalmia is known to exist decreased both morbidity and mortality, improved haemoglobin levels (SOMMER et al., 1986; MUHILAL et al., 1988), and stimulated growth (WEST et al., 1988).

Infection and plasma retinol

A common observation in measles and in other acute/febrile conditions such as chicken-pox, upper respiratory tract infections, bronchitis (ARROYAVE & CALCANO, 1979), diarrhoea, protein energy malnutrition (DARNTON-HILL, 1988), and malaria (Singkamani & Thurnham, unpublished observations) is low circulating concentrations of retinol and retinol-binding protein (RBP). The low retinol concentration is probably linked to the acute phase response, for an early consequence of infection is an increase in vascular endothelial permeability with a consequent fall in the concentrations of albumin, pre-albumin and RBP (KOJ, 1985). A reduction in retinol concentration, therefore, is probably a mechanical response to the changes in vascular permeability. This is supported by some studies by my colleagues and I on rural and urban Thai adults, where we were looking at the effect of malaria on plasma retinol; we found the differences between mean plasma retinol levels in malaria patients and matched controls (0.6 μmol/litre) were very similar in both rural and urban groups. In the urban group, where retinol concentrations in the controls were high, all malaria patients still had retinol concentrations within the normal range; however, in the rural patients, whom we assumed were like their controls in having lower initial concentrations, 30% had plasma retinol levels below 0.35 μmol/litre (Singkamani & Thurnham, unpublished observations). Changes accompanying the acute phase response are normally protective and there may be a survival advantage in some circumstances to be achieved by reducing retinol in the circulation. Vitamin A supplementation, however, has been recommended for children with measles in areas where deficiencies are known to occur (WHO/UNICEF, 1987). Is this necessary?

Although widely used, the concentration of plasma retinol is not a good indicator of nutritional status unless it is around 0.35 μmol/litre (10 μg/dl) or below, when it indicates that liver stores of vitamin A are dangerously low (OLSON, 1981). Retinol concentrations in measles cases in Third World countries are frequently of this order (VARAVITHYA et al., 1986; BHASKARAM et al., 1984; MARKOWITZ et al., 1989), but very few studies have been done where they have been measured before infection occurred. It is generally assumed that when plasma retinol is less than 0.35 μmol/litre patients are at risk of vitamin A deficiency. However, in a longitudinal study in Indian children aged 5 years and below, BHASKARAM (1985) found that retinol concentrations fell approximately 36% in samples collected 2–7 days before measles, to a mean value of 0.038 μmol/litre, including a proportion who were supposedly vitamin A deficient. However retinol concentrations returned to pre-measles levels within 8 weeks without any nutritional intervention. Serum RBP levels closely followed the retinol. Thus, low concentrations of plasma retinol in many infections, rapid changes in plasma concentrations of retinol and RBP, and spontaneous correction on recovery, are suggestive of a metabolic adjustment to the disease but there is evidence to suggest both increased requirements of vitamin A and adverse effects of low retinol levels accompanying infectious diseases, particularly measles.

Synergism between vitamin A deficiency and infection

The synergism between vitamin A deficiency and infection is widely recognized in both animals and man, and nowhere is it more strikingly obvious than in measles. OOMEN et al. (1964) have suggested that, of the febrile diseases of childhood, measles is the one most frequently followed by xerophthalmia. The reason for this may be due to the severe desquamation which occurs during a measles episode, possibly increasing tissue requirements for the vitamin and precipitating the deficiency. In addition, where vitamin A status is low, children with measles frequently develop complications in the acute stage and during subsequent convalescence. In another study, in Indian children (BHASKARAM et al., 1984), 23% developed
complications, mainly respiratory and gastrointestinal, during hospitalization, and, in follow-up studies, a further 14% were found to be ill in the subsequent 3 months, which was 10 times the rate in a comparable control group. Secondary infections with herpes simplex virus were reported by workers in Nigeria, who found the virus in corneal scrapings of eye ulcers in 16 of 34 children attending a measles clinic (Whittle et al., 1979). One study which has directly linked poor prognosis with low retinol concentrations in measles was recently reported from Zaire. The overall case mortality among 283 measles patients was 26%, and 58% of them were found to have retinol concentrations below 0.35 µmol/litre. Using multivariate analysis, the authors tested pneumonia on admission, lymphopaenia, and a plasma retinol below 0.175 µmol/litre, for associations with mortality and found low plasma retinol to be most strongly linked with fatal outcome, but only in children under 2 years old (Markowitz et al., 1989). Furthermore, there is evidence that infections which damage the integrity of epithelial tissues may exert a greater drain on vitamin A requirements than other acute diseases. Studies in Brazil, in children receiving vitamin A supplementation, suggest that retinol utilization was greater in children who suffered chicken-pox than others who were similarly treated but who did not get the disease (Campos et al., 1987). Using the relative dose response test to measure liver retinol reserves, 74% of children who were infected had inadequate liver reserves 6 months after the retinol supplement compared to only 10% of those who were not infected.

Respiratory disease and diarrhoea are 2 of the main causes of death in developing countries, and the studies of Sommer and colleagues in Indonesia were deliberately designed to look at the impact of xerophthalmia on these conditions; children with ocular signs of mild xerophthalmia were more likely to die than others in the community and that their vulnerability was probably attributable to higher rates of respiratory and diarrhoeal diseases (Sommer et al., 1983). Milton et al. (1987) also found that children with mild xerophthalmia developed respiratory problems twice as often as children with normal eyes. Sommer et al. (1987) also found that children with respiratory disease and diarrhoea were more likely to get xerophthalmia. As it is to be expected, there are many children in the such communities, other than those with eye signs, who have poor vitamin A status. Supplementation of children in such communities with vitamin A improves health, reduces mortality and is also accompanied by improved growth and raised concentrations of blood retinol and haemoglobin (Solon et al., 1978; Muhilal et al., 1988; West et al., 1988), while fortification of food has the additional advantage of increasing breast milk retinol levels (Muhilal et al., 1988).

Vitamin A protection at the cellular level

At the cellular level, the effects of vitamin A deficiency are most readily seen in those differentiating tissues which have a rapid turnover such as epithelial tissues of respiratory passages, urinary tract, eyes, buccal cavity and ducts of various glands. In deficiency, horn degeneration, keratinization and metaplasia occur. Epithelial tissues become dry and rough. Ciliated cells are replaced by keratinized cells. The ability to clear surfaces of microorganisms and debris is impaired. Vitamin A is necessary for the production of mucopolysaccharide, an essential glycoprotein secreted by mucous membranes. Mucus provides bacteriostatic protection by its texture and content of lysozyme, secretory immunoglobulin A, etc. Lysozyme is a hydrolytic enzyme effective against certain bacteria and viruses, and its impaired secretion in vitamin A deficiency has been reported in serum, leucocytes, tears, saliva, and the gastrointestinal tract (Neumann, 1977).

It is well established that lowered immunoresponsiveness is a sign of vitamin A deficiency (Wolf, 1980; Zile et al., 1979; Hof & Wirsing, 1979), but the effects on cell-mediated immunity (CMI) may be greater than those on humoral immunity (Bhaskaran, 1985). Humoral immunity is poorly developed in young children and they depend to a much larger extent on CMI. The production of reactive oxygen species (ROS), which kill invading organisms by oxidative damage, is an important component of CMI. To prevent damage to host tissues, the body has an elaborate antioxidant defence system (Thurnham, 1989). Structural integrity of tissues is one of the first lines of defence. A breakdown in integrity of epithelial tissues is one of the early facets of vitamin A deficiency. Thus tissues in the young child with xerophthalmia may be more vulnerable to damage during infection, particularly as levels of plasma retinol fall, the greater reliance on CMI for immunoprotection may additionally contribute to the pathological insults on vulnerable tissues. Furthermore, the lack of dietary carotenes, the main source of vitamin A in the third World, may also contribute to impaired antioxidant defence as this is also believed to be a function of carotenes in tissue.

Vitamin A, iron and haemoglobin

The interesting observation that haemoglobin levels improve following vitamin A supplementation has been reported from several countries (Forte, 1986; Milton et al. 1987; West et al., 1988). Infection and the acute phase response may also be responsible for this association. A consequence of infection is an increased production of acute phase reactants in the circulation, including ferritin, caeruloplasmin, lactoferrin, haptoglobin, haemopexin, etc., and a reduction in ascorbate and transferrin (Keusch, 1984; Thurnham, 1989). These changes, which reduce the likelihood of ferrous iron formation (which can cause oxidative damage) and lower the amount of circulating iron during infection, may also depress haemoglobin formation. The anaemia of chronic infection is well recognized. Vitamin A repletion will reverse these effects and stimulate haemoglobin synthesis by assisting in the recovery from infection and by thus appearing to increase iron mobilization, as suggested by Mejia et al. (1979).

Conclusions

Vitamin A is necessary for the control and differentiation of epithelial tissues, and infections most closely associated with vitamin A deficiency are those in which structure, function or protection of epithelium may be impaired—namely measles, respiratory disease, and diarrhoea. Feburil infections are associ-
ated with low circulating levels of retinol, and while these may be a consequence of the acute phase response, where the initial vitamin A status is poor, the very low levels produced may impair recovery and be associated with fatal outcome in young children. Vitamin A supplementation benefits not only those with ocular symptoms but many others in the same community. The effectiveness of combining treatment of the diseases listed above with retinol supplementation in areas where vitamin A status is low appears to be highly desirable, but a long-term solution to vitamin A inadequacy must be achieved by improving diet, not supplementation or fortification of foods.

References


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