

Review Article

Role of vitamin A supplementation in the treatment of tuberculosis

MURLI L. MATHUR

ABSTRACT

Vitamin A deficiency has been commonly observed in patients with tuberculosis. Low serum retinol levels return to normal after antituberculosis treatment even when no supplements are provided. The deficiency of vitamin A observed in patients with tuberculosis might have contributed to the development of tuberculous disease in them. Alternatively, deficiency could be the result of loss of appetite, poor intestinal absorption, increased urinary loss of vitamin A or acute phase reaction in TB. Vitamin A deficiency lowers immunity while vitamin A supplementation reduces morbidity and mortality, particularly from measles and diarrhoea. Vitamin A supplementation also decreases the mortality rate in HIV-infected children and delays the progression of HIV disease in infected subjects. A higher incidence of lung cancer and increased mortality have been observed in smokers after beta-carotene supplementation. Zinc deficiency is also common in tuberculosis, which may impose a secondary vitamin A deficiency. Clinical trials have shown conflicting results regarding the effect of supplementation of vitamin A, alone or with other micronutrients, on time taken to sputum conversion in patients with pulmonary tuberculosis. Supplementation with multiple micronutrients (including zinc) rather than vitamin A alone may be more beneficial in patients with tuberculosis, but clinical trials on such a combination are lacking.

Natl Med J India 2007;20:16–21

INTRODUCTION

Vitamin A deficiency has been found to be associated with many infectious diseases.¹ A high prevalence of vitamin A deficiency has been observed in patients with pulmonary tuberculosis (TB),^{2–9} which is more pronounced in those co-infected with HIV.^{2,5,8} This indicates an association between vitamin A deficiency and TB. A few studies have shown that low vitamin A levels return to normal after antituberculosis treatment (ATT) even in the absence of vitamin A supplementation.^{4,5,10} To assess the possible role of vitamin A supplementation in the treatment of patients with TB, the available evidence was reviewed.

VITAMIN A LEVELS AND TUBERCULOSIS

A serum retinol level of $<0.70 \mu\text{mol/L}$ ($20 \mu\text{g/dl}$) is currently used as the cut-off for determining vitamin A deficiency.^{11,12} The best way to study the nature of the association between vitamin A deficiency and TB would be a cohort study. There is only one such study by Getz *et al.*¹³ in the 1940s which included 1100 men who were followed for 5 years and did not have TB at the start of the study. Clinical, radiological and laboratory evaluations were done over this period and 16 men developed TB. Of these, 13 men (81.3%) had consistently low plasma vitamin A levels, while only 317 of 1058 (30%) who remained free from TB had low vitamin A levels¹³ (relative risk=2.70; 95% CI: 2.10–3.48; $p=0.00001$). Exposure to TB did not differ between men who developed TB and those who did not. This cohort study showed a higher probability of developing TB in vitamin A-deficient subjects, indicating their higher susceptibility to TB disease.

Hanekom *et al.*³ found low plasma vitamin A levels to be associated with more extensive or severe disease, and low levels of retinol-binding protein (RBP), prealbumin and albumin. They also found that high dose vitamin A supplementation had no effect on the outcome of the disease. Ramachandran *et al.*⁴ also found lower serum vitamin A levels in patients with pulmonary TB; these levels increased following ATT but without vitamin A supplementation. Mugusi *et al.*⁵ also observed lower serum vitamin A levels in patients with pulmonary TB, which increased after 2 months of ATT in HIV-negative cases but not in HIV-positive ones. Karyadi *et al.*⁶ and van Lettow *et al.*² showed that retinol levels were markedly low in patients with pulmonary TB with wasting (wasting was defined as a body mass index $<18.5 \text{ kg/m}^2$). Koyanagi *et al.*⁷ found lower serum concentrations of retinol and zinc in patients with pulmonary TB as compared with healthy volunteers. In their study, patients with pulmonary TB with higher levels of C-reactive protein (CRP $>50 \text{ mg/L}$)—indicative of an acute phase reaction (APR)—had lower serum concentrations of retinol and zinc than those with lower CRP concentrations. Rwangabwoba *et al.*⁸ from Rwanda reported that 29% of patients with TB who were HIV-positive had serum vitamin A levels $<1.05 \mu\text{mol/L}$. Women had lower levels than men and patients with recent weight loss had lower vitamin A levels than those without weight loss.

These studies have shown that in developing countries patients with TB, especially those with wasting and/or HIV infection, have low vitamin A levels. This could be because patients with vitamin A deficiency have an increased risk of

Desert Medicine Research Centre, New Pali Road, Jodhpur 342005, Rajasthan, India; murlimathur@dmrcjodhpur.org, murlimathur@gmail.com

developing TB, as observed by Getz *et al.*,¹³ or because development of active TB may decrease plasma vitamin A levels. The first hypothesis can be tested only by cohort studies that include healthy subjects till a proportion of them develop TB. Such studies are lacking. The mechanism by which lowered serum retinol has an effect on TB may be related to (i) poor dietary intake due to loss of appetite, ignorance or inability to afford green leafy vegetables and fruits, (ii) poor absorption of vitamin A from the intestine, (iii) increased excretion of vitamin A in the urine¹⁴⁻¹⁶ (impaired tubular reabsorption of low molecular weight proteins such as RBP appears to be a cause of urinary retinol loss¹⁵), (iv) a transient reduction in the transcription of messenger RNA, resulting in decreased release of RBP from the liver into the blood,¹⁷ or (v) an increased uptake of retinol by specific target tissues.¹⁸ The last two responses may be initiated by inflammatory cytokines which are produced early in response to the infectious stimulus,^{19,20} though the relationship between acute phase proteins and serum/plasma vitamin A levels has not been considered in the above studies.

ACUTE PHASE REACTION AND PLASMA VITAMIN A LEVELS

Positive acute phase proteins are defined as proteins whose concentration increases by 25% or more during infection, inflammation or trauma.²¹⁻²³ The precise effect of the APR on the metabolism of vitamin A is unclear, but it is well documented that infections result in lowered serum retinol levels and hepatic vitamin A stores.²⁴ An APR is known to occur during the course of TB and levels of most acute phase proteins increase while those of others (e.g. transferrin) decrease.²⁵ The levels of acute phase proteins gradually fall with treatment.²⁶⁻²⁸ This might be the reason for the rise in vitamin A levels in patients with TB after treatment, and has been observed in patients who are HIV-negative⁵ and do not smoke.⁹

RBP is a negative acute phase protein that is a serum carrier protein for vitamin A. The low vitamin A levels observed in TB are likely to be due to reduced RBP concentration which results in impairment of the hepatic release of vitamin A. A meta-analysis by Thurnham *et al.*²⁹ showed that plasma retinol concentration is affected by levels of acute phase proteins. The former is much higher in people with normal concentrations of acute phase proteins than in those with raised concentrations. They recommended that while interpreting plasma retinol concentrations, these values should be corrected using serum CRP and alpha 1-acid glycoprotein concentrations.²⁹ Similar observations have been made by Stephensen and Gildengorin.³⁰ It is therefore necessary to consider the level of CRP and extent of activation of the APR while interpreting serum vitamin A concentrations in patients with TB.⁷ Thurnham *et al.*²⁹ analysed data from 15 studies on concentrations of plasma retinol and one or more acute phase proteins (α 1-acid glycoprotein, α 1-antichymotrypsin, CRP or serum amyloid A) and found retinol levels to be much higher in people with normal concentrations of acute phase protein than in those with raised concentrations. The reduction in plasma retinol level among individuals with infection compared with healthy individuals was 13% (during the incubation phase), 24% (early convalescence) and 11% (late convalescence). Estimates of vitamin A deficiency in individuals without raised acute phase proteins (healthy group) were the same as those obtained by adjustment of plasma retinol concentrations in the whole group. They suggested that when amounts of α 1-antichymotrypsin and α 1-acid glycoprotein are

higher than their respective thresholds, plasma retinol concentrations should be increased by 16%–19% to compensate for subclinical infection. Karyadi *et al.*⁶ found that plasma retinol concentration did not correlate with CRP in patients with TB and presented the argument that CRP is an acute phase protein whose concentration changes rapidly as a result of infection. Thus, CRP may not provide an accurate assessment for acute phase changes in plasma retinol during a chronic illness such as TB, as low plasma retinol in such patients may be the result of a primary deficiency. These studies suggest that the vitamin A deficiency observed in patients with TB is partly due to the APR and may not be an indication for vitamin A supplementation (Table I).

VITAMIN A SUPPLEMENTATION

Table II details the results of some studies on serum vitamin A level after ATT with and without vitamin A supplementation in patients with pulmonary TB. Karyadi *et al.*³¹ reported a rise in plasma retinol concentrations, earlier sputum conversion and faster resolution of radiological lesions following vitamin A and zinc supplementation during ATT. In those who received supplementation, the increase in plasma retinol concentration correlated with a reduction in the mean lesion area after 6 months of ATT. No other study has shown a beneficial effect of vitamin A supplementation in pulmonary TB. Hanekom *et al.*³ did not observe any effect of high dose vitamin A therapy on disease outcome in South African children with TB. Range *et al.*^{33,34} have shown that vitamin A and other vitamin and mineral supplementation does not improve sputum conversion and overall survival in patients with pulmonary TB. It has also been observed that in patients with pulmonary TB receiving ATT vitamin A levels tend to normalize even when vitamin A supplementation is not given^{4,5,10,31} suggesting that supplementation may not be necessary. On the other hand, adverse effects of beta-carotene supplementation in the form of a higher incidence of lung cancer and higher mortality have been reported.

The alpha-tocopherol, beta-carotene (ATBC) cancer prevention study³⁵ was a randomized, double-blind, placebo-controlled, primary prevention trial done to assess whether supplementation with alpha-tocopherol, beta-carotene or both would reduce the incidence of lung cancer in male smokers. Among men who received beta-carotene, an excess cumulative incidence of lung cancer was observed after 18 months, which increased progressively thereafter. The total mortality was higher among those who received beta-carotene, primarily because there were more deaths from lung cancer and ischaemic heart disease.³⁵ In the beta-carotene and retinol efficacy trial (CARET),³⁶ the effect of a combination of 30 mg of beta-carotene per day and 25 000 IU of retinol (vitamin A) per day in the form of retinyl palmitate for about 4 years was evaluated in smokers, former smokers and workers exposed to asbestos. The results showed significantly higher post-intervention risk of lung cancer and all-cause mortality for the intervention group compared with the placebo group. The risks remained higher even after 5 years of stopping the intervention though at that time the difference was not statistically significant.³⁷ An important clue about this negative interaction emerged from a small randomized trial of moderate dose 13-*cis*-retinoic acid in subjects who had evidence of metaplasia of the lung, an early premalignant lesion. Lee *et al.*³⁸ showed that while the retinoid was ineffective in reversing the premalignant lesion in individuals who continued smoking, there was a cooperative effect between

TABLE I. Results of studies on serum vitamin A levels in patients of pulmonary tuberculosis (TB)

Author (year)	Prevalence of vitamin A deficiency (retinol <0.70 µmol/L, i.e. <20 µg/dl)	Mean serum/plasma vitamin A level	Study subjects
Hanekom <i>et al.</i> ³ (1997)	62%	18.1 (10.3) µg/dl	South African children with pulmonary TB
van Lettow <i>et al.</i> ² (2004)	58.6% in HIV-negative cases; 57.3%–66.7% in HIV-positive cases	0.636 (0.367, 1.104) µmol/L in HIV-negative cases; 0.522–0.603 µmol/L in HIV-positive cases	Patients of pulmonary TB in Malawi (222 HIV-negative and 579 HIV-positive cases)
Ramachandran <i>et al.</i> ⁴ (2004)	81% patients of pulmonary TB had serum vitamin A <30 µg/dl	21.2 µg/dl in pulmonary TB compared with 42.2 µg/dl in their own household contacts and 48.1 µg/dl in normal healthy subjects	Patients of pulmonary TB (47), healthy contacts of TB cases (46) and healthy normal subjects (30) from south India
Mugusi <i>et al.</i> ⁵ (2003)	89.7% in HIV-negative cases of pulmonary TB (35/39); 90.1% in HIV-positive cases of pulmonary TB (55/61); 9.1% in HIV-negative blood donors (9/99); 64.4% in HIV-positive blood donors (29/45)	15.0 (3.9) µg/dl in HIV-negative cases of pulmonary TB; 13.1 (5.6) µg/dl in HIV-positive cases of pulmonary TB; 26.6 (5.4) in HIV-negative blood donors; 18.8 (5.7) in HIV-positive blood donors	100 patients of pulmonary TB and 144 blood donors in Tanzania
Karyadi <i>et al.</i> ⁶ (2000)	33% in pulmonary TB and 13% in controls	0.89 (0.4) µmol/L compared with 1.09 (0.6) µmol/L in healthy controls (group with BMI <18.5); 1.22 (0.5) µmol/L compared with 1.32 (0.6) µmol/L in healthy controls (group with BMI >18.5)	41 pulmonary TB patients and 41 healthy controls from Indonesia
Rwangabwoba <i>et al.</i> ⁸ (1998)	29% had serum vitamin A levels <1.05 µmol/L	1.42 (0.63) µmol/L	94 HIV-positive patients of pulmonary TB from Rwanda
Madebo <i>et al.</i> ⁹ (2003)	—	0.90 (0.80, 0.99) µmol/L in pulmonary TB patients; 2.49 (2.25, 2.73) in healthy Ethiopians; 2.33 (2.19, 2.47) in healthy Norwegians	125 patients of pulmonary TB from Ethiopia, 45 healthy blood donors from Ethiopia and 25 healthy Norwegian blood donors

retinoid and smoking cessation in the lungs of those individuals who stopped smoking; these individuals had improvement in metaplasia, upregulation of retinoic acid receptor-beta (RARβ)³⁹ and downregulation of proliferation.⁴⁰ These findings showed that in smokers, former smokers and non-smokers the effects of retinoids and certain carotenoids were different. It can be extrapolated that for vitamin A supplementation to be beneficial in TB it should be accompanied by cessation of smoking; otherwise it may even be harmful.

VITAMIN A AND ZINC

The fact that Karyadi *et al.*³¹ found a combination of vitamin A and zinc supplementation beneficial in TB and Hanekom *et al.*³ did not find any beneficial effect of vitamin A therapy in children with TB might indicate an important role for zinc deficiency, which is also common in patients with TB.^{2,41–46} Serum zinc levels are low in patients with TB and increase with ATT.^{41,44} Christian and West⁴⁷ reviewed the interactions of vitamin A and zinc in cross-sectional, observational and supplementation clinical trials, and concluded that zinc deficiency could impose a secondary vitamin A deficiency in protein–energy deficient populations. This might be the explanation for the observation of a strong association between vitamin A deficiency and wasting in patients with TB.^{2,8} Zinc has been shown to be essential in vitamin A metabolism as it is required for mobilization of vitamin A from the liver. Two common mechanisms postulated to explain this dependence relate to the regulatory role of zinc in vitamin A transport mediated through protein synthesis; and the oxidative conversion of retinol to retinal, which requires the

action of a zinc-dependent retinol dehydrogenase enzyme.⁴⁷ During the APR, plasma zinc and iron levels also decrease due to hepatic sequestration. Decreased retinol levels may be caused by reduced mobilization of RBP from the liver due to zinc deficiency, as RBP is a zinc-dependent protein.²⁰

Circulating and hepatic concentrations of retinol have been observed to fall and rise in experimental zinc deficiency and repletion, respectively, in animals fed adequate amounts of vitamin A.⁴⁷ Therefore, supplementation with vitamin A may not be beneficial in TB without correction of the zinc deficiency. This may be the reason for the observation of Mahalanabis⁴⁸ that vitamin A supplementation did not benefit children with acute lower respiratory tract infection though zinc supplementation did. It is worth mentioning here that zinc deficiency affects about one-third of the world's population.⁴⁹ In a clinical trial conducted by Range *et al.*^{33,34} the group that received zinc was not given a vitamin A supplement, and the group that received all vitamins and minerals was not given zinc, which might be the reason for not finding a beneficial effect in either of the two groups. On the other hand, Karyadi *et al.*³¹ used zinc and vitamin A supplementation simultaneously and demonstrated a beneficial effect.

POSSIBLE MECHANISM OF EFFECT OF VITAMIN A IN TUBERCULOSIS

Infection with *Mycobacterium tuberculosis* is very common in India but only a few develop active disease. It is the individual's immune response that decides whether the bacteria engulfed by alveolar macrophages are killed, contained or multiply, leading

TABLE II. Results of studies on serum vitamin A level after antituberculosis therapy (ATT) with and without vitamin A supplementation in patients of pulmonary tuberculosis (TB)

Author (year)	Intervention	Results of follow up after few months of ATT
Karyadi <i>et al.</i> ³¹ (2002)	Micronutrient group (n=40) received 1500 retinol equivalents (5000 i.u.) vitamin A (as retinyl acetate) and 15 mg Zn (as zinc sulphate) daily for 6 months. Placebo group (n=40). Both groups received ATT.	Sputum conversion (p<0.05) and resolution of X-ray lesion (p<0.01) occurred earlier in the micronutrient group; retinol level increased in both groups.
Hanekom <i>et al.</i> ³ (1997)	High-dose vitamin A and ATT was given.	High-dose vitamin A had no effect on disease outcome.
Chandra ³² (2004)	One group received 400 µg vitamin A, 14 mg zinc and some other micronutrients; placebo group received calcium; ATT was given to both groups.	Higher sputum conversion at 2 months and 3 months in supplementation group; sample size very small and limited power of study.
Range <i>et al.</i> ³³ (2005)	One group given multi-micronutrient (vitamin A 5000 i.u., vitamin B1 20 mg, vitamin B2 20 mg, vitamin B6 25 mg, vitamin B12 50 µg, folic acid 0.8 mg, niacin 40 mg, vitamin C 200 mg, vitamin E 60 mg, vitamin D3 200 i.u., selenium 0.2 mg and copper 5 mg) supplementation and the other group given zinc (45 mg). Effect of both compared with placebo. Randomized, double-blind, placebo-controlled two-by-two trial in Tanzania. ATT was given to both groups.	Compared to placebo, neither multi-micronutrient nor zinc supplementation had significant effects on culture conversion, but multi-micronutrient supplementation increased weight gain in TB patients.
Range <i>et al.</i> ³⁴ (2006)	Pulmonary TB patients (499) were randomized, using a two-by-two factorial design, to Zn (45 mg) or placebo, and multivitamin-mineral (MVM=vitamins A, B, C, D, E, and selenium and copper) or placebo. Survival status was ascertained at the end of the 8-month ATT and supplementation period.	No effects of MVM (relative risk [RR] 0.73; 95% CI: 0.43, 1.23) and Zn (RR: 0.76; 95% CI: 0.46, 1.28). In HIV-positive patients, marginally significant effects of both MVM (RR: 0.60; 95% CI: 0.34, 1.05) and Zn (RR: 0.63, 95% CI: 0.37, 1.08) were seen, and MVM and Zn combined reduced mortality (RR: 0.29; 95% CI: 0.10, 0.80; interaction ratio 0.52).
Ramachandran <i>et al.</i> ⁴ (2004)	Vitamin A supplementation was not given. ATT was given.	Serum vitamin A levels increased in 31 (93%) of 37 patients. Mean level increased from 21.0 µg/dl (8.9–38.2) to 38.9 µg/dl (13.6–75.2) after treatment (p<0.001).
Mugusi <i>et al.</i> ⁵ (2003)	Vitamin A supplementation was not given. ATT was given.	Mean serum vitamin A level increased from 15.0 (3.9) µg/dl to 22.3 (5.1) µg/dl in HIV-negative cases of pulmonary TB (p<0.0001). Mean serum vitamin A level showed a small decline from 13.1 (5.6) µg/dl in HIV-positive cases of pulmonary TB (p=0.14).
Wiid <i>et al.</i> ¹⁰ (2004)	Vitamin A supplementation was not given. ATT was given.	Mean serum vitamin A level increased (p<0.001).

to a flare-up of the infection and development of disease. The effect of vitamin A on an individual's immunity against TB is possibly the key issue. Layton and Youmans⁵⁰ quantitatively altered the vitamin A component of a synthetic diet to determine its effect on the resistance of albino mice to infection with *Mycobacterium tuberculosis*. The animals were challenged after the first 2 weeks of feeding and the percentage that survived acute death was determined. Vitamin A concentrations ranging from 0 to 320 000 units/kg of diet were studied in 4 experiments. Vitamin A enhanced survival when it was increased from the normal level of 20 000 units/kg of diet to 160 000 units, but further increase reduced survival. However, excessive levels were not toxic for the animals, since the controls gained weight normally and appeared healthy. The alterations in vitamin A had no effect on animal weight. In a similar experiment, the effect of dietary vitamin A on T cell proliferation was studied in chicks.⁵¹ Addition of small amounts of vitamin A enhanced the T cell proliferative response, which increased with dietary vitamin A supplementation until the diet contained 6660 µg/kg; above this the response decreased. In animal studies, vitamin A deficiency induces a shift from type 2 (humoral) to type 1 (cellular) cytokines,⁵² which is desirable in TB. Animal studies have also shown that supplementation with vitamin A above dietary requirements enhances inflammatory responses

accompanied by decreasing helper T (Th)-1 cells.⁵³ The vitamin A metabolite, retinoic acid, affects Th-1 and Th-2 development. This effect is partly exerted through the modulation of antigen-presenting cell functions. Retinoic acids also exert direct effects on the T cells to suppress Th-1 development and enhance Th-2 development via retinoic acid receptors.⁵⁴ Supplementation with very high doses of vitamin A may therefore suppress Th-1 development, which is not desirable in TB.

In vitro studies have shown that retinoic acid can inhibit multiplication of mycobacteria in the macrophages.⁵⁵ In human studies, vitamin A deficiency has been found to be associated with a relative type 1 cytokine dominance and proportionately more natural killer (NK) cells,^{52,56} both of which may be somewhat beneficial to persons who are exposed to *M. tuberculosis*, HIV or other intracellular organisms requiring a type 1 immune response.⁵⁷ Interestingly, vitamin A deficiency is also associated with BCG vaccine scarring.⁵² Scarring after BCG vaccination is associated with type 1 cytokines at the vaccination site, which are indicative of a type 1 immune response to the vaccine.^{58,59} Increased numbers of Th and T-inducer lymphocytes have been reported in human adults given oral beta-carotene supplementation.^{60,61} The number of lymphoid cells with surface markers for NK cells and for interleukin (IL)-2 and transferrin receptors was also increased substantially in peripheral blood

mononuclear cells in individuals who had received beta-carotene supplements.^{60,62} Enhanced NK cell cytotoxicity was observed in human subjects given oral beta-carotene.⁶³ Similarly, long term beta-carotene supplementation in elderly (but not middle-aged) men increased NK cell activity.⁶⁴ In one study⁶⁵ of immunodeficient patients, many of whom were vitamin A deficient, vitamin A supplementation led to a shift toward a type 2 profile, with increased production of IL-10 and immunoglobulin A (IgA) in plasma and IgG *in vitro*, and decreased the production of tumour necrosis factor alpha (TNF- α), a proinflammatory type 1 cytokine in plasma. Plasma-soluble CD30 (sCD30) is the result of proteolytic splicing from the membrane-bound form of CD30, a putative marker of type 2 cytokine-producing cells. Hanekom *et al.* found high sCD30 levels in children with TB, which may reflect the presence of a type 2 cytokine response. Nutritional compromise was associated with higher sCD30 levels and vitamin A therapy resulted in sCD30 levels decreasing towards normal over time,⁶⁶ while the sCD30 level also increased with time in those who did not receive vitamin A supplementation. From the available evidence, it seems that vitamin A can improve immunity specifically against TB, but high doses may be harmful.

CONCLUSION

Many studies have shown that patients with pulmonary TB have vitamin A deficiency. However, these studies have not taken account of the APR while interpreting vitamin A levels in serum/plasma. In patients with TB it is nearly impossible to accurately determine the vitamin A status prior to the onset of TB. Hence, it is difficult to know whether the vitamin A deficiency led to TB or TB led to vitamin A deficiency due to loss of appetite, poor intestinal absorption and increased urinary loss. Patients with advanced disease are more likely to be unemployed and, therefore, it is also likely that socioeconomic factors contribute to a poorer micronutrient intake in these patients. The vitamin A deficiency observed in patients with TB may be an indicator of the effect of a humoral reaction to TB. Zinc has been shown to be essential in vitamin A metabolism as it is required to mobilize vitamin A from the liver.⁶⁷ Zinc deficiency also affects the host defence in a variety of ways. It results in decreased phagocytosis and leads to a reduced number of circulating T cells and reduced tuberculin (purified protein derivative [PPD]) reactivity, at least in animals.⁶⁸ These observations suggest that zinc deficiency could both precipitate health consequences associated with vitamin A deficiency and, through its gate-keeping role, lead to a secondary vitamin A deficiency in human populations. Furthermore, zinc supplementation of marginally nourished groups might be expected to improve both zinc and vitamin A status and associated health outcomes. Although vitamin A deficiency could also interfere with zinc efficacy, data to support this interaction are sparse. Clear evidence is lacking of the benefits of vitamin A supplementation in TB in the absence of zinc supplementation in humans. Some studies have shown that vitamin A deficiency in TB is strongly associated with wasting. Malnutrition predisposes to TB, and TB causes 'consumption', and vitamin A deficiency is more pronounced in patients with TB and wasting.^{2,8} This suggests that supplementation with multiple micronutrients (including zinc) rather than vitamin A alone may be more beneficial in TB. In a small study, Chandra³² showed better sputum conversion with ATT supplemented with multivitamin-trace elements. Range *et al.*^{33,34} in a clinical

trial showed that supplementation of multiple micronutrients including vitamin A (but not zinc) every day for 2 months and then biweekly for 4 months did not have any effect on the sputum culture conversion rate of patients with pulmonary TB. In the absence of evidence of the beneficial effect of vitamin A supplementation alone, interventions that include both vitamin A and zinc may be a better choice, and should be accompanied by cessation of smoking.

REFERENCES

- 1 Scrimshaw NS, Taylor CE, Gordon JE. *Interactions of nutrition and infection*. Geneva, Switzerland: World Health Organization; 1968.
- 2 van Lettow M, Harries AD, Kumwenda JJ, Zijlstra EE, Clark TD, Taha TE, *et al.* Micronutrient malnutrition and wasting in adults with pulmonary tuberculosis with and without HIV co-infection in Malawi. *BMC Infect Dis* 2004;**4**:61.
- 3 Hanekom WA, Potgieter S, Hughes EJ, Malan H, Kessow G, Hussey GD. Vitamin A status and therapy in childhood pulmonary tuberculosis. *J Pediatr* 1997;**131**:925-7.
- 4 Ramachandran G, Santha T, Garg R, Baskaran D, Iliayas SA, Venkatesan P, *et al.* Vitamin A levels in sputum-positive pulmonary tuberculosis patients in comparison with household contacts and healthy 'normals'. *Int J Tuberc Lung Dis* 2004;**8**:1130-3.
- 5 Mugusi FM, Rusizoka O, Habib N, Fawzi W. Vitamin A status of patients presenting with pulmonary tuberculosis and asymptomatic HIV-infected individuals, Dar es Salaam, Tanzania. *Int J Tuberc Lung Dis* 2003;**7**:804-7.
- 6 Karyadi E, Schultink W, Nelwan RH, Gross R, Amin Z, Dolmans WM, *et al.* Poor micronutrient status of active pulmonary tuberculosis patients in Indonesia. *J Nutr* 2000;**130**:2953-8.
- 7 Koyanagi A, Kuffo D, Gresely L, Shenkin A, Cuevas LE. Relationships between serum concentrations of C-reactive protein and micronutrients, in patients with tuberculosis. *Ann Trop Med Parasitol* 2004;**98**:391-9.
- 8 Rwangabwoba JM, Fischman H, Semba RD. Serum vitamin A levels during tuberculosis and human immunodeficiency virus infection. *Int J Tuberc Lung Dis* 1998;**2**:771-3.
- 9 Madebo T, Lindtjorn B, Aukrust P, Berge RK. Circulating antioxidants and lipid peroxidation products in untreated tuberculosis patients in Ethiopia. *Am J Clin Nutr* 2003;**78**:117-22.
- 10 Wiid I, Seaman T, Hoal EG, Benade AJ, Van Helden PD. Total antioxidant levels are low during active TB and rise with anti-tuberculosis therapy. *IUBMB Life* 2004;**56**:101-6.
- 11 de Pee S, Dary O. Biochemical indicators of vitamin A deficiency: Serum retinol and serum retinol binding protein. *J Nutr* 2002;**132**:2895S-2901S.
- 12 Sommer A, Davidson FR. Assessment and control of vitamin A deficiency: The Anney accords. *J Nutr* 2002;**132**:2845S-2850S.
- 13 Getz HR, Long ER, Henderson HJ. A study of the relation of nutrition to the development of tuberculosis: Influence of ascorbic acid and vitamin A. *Am Rev Tuberc* 1951;**64**:381-93.
- 14 Ross AC. Vitamin A status: Relationship to immunity and the antibody response. *Proc Soc Exp Biol Med* 1992;**200**:303-20.
- 15 Mitra AK, Alvarez JO, Guay-Woodford L, Fuchs GJ, Wahed MA, Stephensen CB. Urinary retinol excretion and kidney function in children with shigellosis. *Am J Clin Nutr* 1998;**68**:1095-103.
- 16 Stephensen CB, Alvarez JO, Kohatsu J, Hardmeier R, Kennedy JJ Jr, Gammon RB Jr. Vitamin A is excreted in the urine during acute infection. *Am J Clin Nutr* 1994;**60**:388-92.
- 17 Rosales FJ, Ritter SJ, Zolfaghari R, Smith JE, Ross AC. Effects of acute inflammation on plasma retinol, retinol binding protein, and its mRNA in the liver and kidneys of vitamin A-sufficient rats. *J Lipid Res* 1996;**37**:962-71.
- 18 Willumsen JF, Simmank K, Filteau SM, Wagstaff LA, Tomkins AM. Toxic damage to the respiratory epithelium induces acute phase change in vitamin A metabolism without depleting retinol stores of South African children. *J Nutr* 1997;**127**:1339-443.
- 19 Kushner I. Regulation of the acute phase response by cytokines. *Perspect Biol Med* 1993;**36**:611-12.
- 20 Raynes JG. The acute phase response. *Biochem Soc Trans* 1994;**22**:69-74.
- 21 Frieden TR, Sowell AL, Henning KJ, Huff OL, Gunn RA. Vitamin A levels and severity of measles, New York City. *Am J Dis Child* 1992;**146**:182-6.
- 22 Hussey GO, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. *N Engl J Med* 1990;**323**:160-4.
- 23 Coutsoudis A, Broughton M, Coovadia HM. Vitamin A supplementation reduces measles morbidity in young African children: A randomized, placebo-controlled, double-blind trial. *Am J Clin Nutr* 1991;**54**:890-5.
- 24 Campos FA, Flores H, Underwood BA. Effect of an infection on vitamin A status of children as measured by the relative dose response (RDR). *Am J Clin Nutr* 1987;**46**:91-4.
- 25 Immanuel C, Acharyulu GS, Kannapiran M, Segaran R, Sarma GR. Acute phase proteins in tuberculous patients. *Indian J Chest Dis Allied Sci* 1990;**32**:15-23.

- 26 Grange JM, Kardjito T, Setiabudi I. A study of acute-phase reactant proteins in Indonesian patients with pulmonary tuberculosis. *Tubercle* 1984;**65**:23–39.
- 27 Wong CT, Saha N. Changes in serum proteins (albumin, immunoglobulins and acute phase proteins) in pulmonary tuberculosis during therapy. *Tubercle* 1990;**71**:193–7.
- 28 Wong CT, Saha N. Serum immunoglobulin and acute phase protein concentrations in pulmonary tuberculosis patients in Singapore. *Trop Geogr Med* 1989;**41**:218–21.
- 29 Thurnham DI, McCabe GP, Northrop-Clewes CA, Nestel P. Effects of subclinical infection on plasma retinol concentrations and assessment of prevalence of vitamin A deficiency: Meta-analysis. *Lancet* 2003;**362**:2052–8.
- 30 Stephensen CB, Gildengorin G. Serum retinol, the acute phase response, and the apparent misclassification of vitamin A status in the third National Health and Nutrition Examination Survey. *Am J Clin Nutr* 2000;**72**:1170–8.
- 31 Karyadi E, West CE, Schultink W, Nelwan RH, Gross R, Amin Z, *et al*. A double-blind, placebo-controlled study of vitamin A and zinc supplementation in persons with tuberculosis in Indonesia: Effects on clinical response and nutritional status. *Am J Clin Nutr* 2002;**75**:720–7.
- 32 Chandra RK. Nutrient supplementation as adjunct therapy in pulmonary tuberculosis. *Int J Vitam Nutr Res* 2004;**74**:144–6.
- 33 Range N, Andersen AB, Magnussen P, Mugomela A, Friis H. The effect of micronutrient supplementation on treatment outcome in patients with pulmonary tuberculosis: A randomized controlled trial in Mwanza, Tanzania. *Trop Med Int Health* 2005;**10**:826–32.
- 34 Range N, Chagalucha J, Krarup H, Magnussen P, Andersen AB, Friis H. The effect of multi-vitamin/mineral supplementation on mortality during treatment of pulmonary tuberculosis: A randomised two-by-two factorial trial in Mwanza, Tanzania. *Br J Nutr* 2006;**95**:762–70.
- 35 The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 1994;**330**:1029–35.
- 36 Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, *et al*. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;**334**:1150–5.
- 37 Goodman GE, Thornquist MD, Balmes J, Cullen MR, Meyskens FL Jr, Omenn GS, *et al*. The Beta-Carotene and Retinol Efficacy Trial: Incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping beta-carotene and retinol supplements. *J Natl Cancer Inst* 2004;**96**:1743–50.
- 38 Lee JS, Lippman SM, Benner SE, Lee JJ, Ro JY, Lukeman JM, *et al*. Randomized placebo-controlled trial of isotretinoin in chemoprevention of bronchial squamous neoplasia. *J Clin Oncol* 1994;**12**:937–45.
- 39 Xu XC, Lee JS, Lee JJ, Morice RC, Liu X, Lippman SM, *et al*. Nuclear retinoid acid receptor beta in bronchial epithelium of smokers before and during chemoprevention. *J Natl Cancer Inst* 1999;**91**:1317–21.
- 40 Khuri FR, Lee JS, Lippman SM, Lee JJ, Kalapurakal S, Yu R, *et al*. Modulation of proliferating cell nuclear antigen in the bronchial epithelium of smokers. *Cancer Epidemiol Biomarkers Prev* 2001;**10**:311–18.
- 41 Ciftci TU, Ciftci B, Yis O, Guney Y, Bilgihan A, Ogretensoy M. Changes in serum selenium, copper, zinc levels and Cu/Zn ratio in patients with pulmonary tuberculosis during therapy. *Biol Trace Elem Res* 2003;**95**:65–71.
- 42 Deveci F, Ilhan N. Plasma malondialdehyde and serum trace element concentrations in patients with active pulmonary tuberculosis. *Biol Trace Elem Res* 2003;**95**:29–38.
- 43 Ray M, Kumar L, Prasad R. Plasma zinc status in Indian childhood tuberculosis: Impact of antituberculosis therapy. *Int J Tuberc Lung Dis* 1998;**2**:719–25.
- 44 Taneja DP. Observations on serum zinc in patients of pulmonary tuberculosis. *J Indian Med Assoc* 1990;**88**:280–1.
- 45 Bogden JD, Lintz DI, Joselow MM, Charles J, Salaki JS. Effect of pulmonary tuberculosis on blood concentrations of copper and zinc. *Am J Clin Pathol* 1977;**67**:251–6.
- 46 Bogden JD, Lintz DI, Joselow MM, Charles J, Salaki JS. Copper/zinc ratios in whole blood, plasma, and erythrocytes in pulmonary tuberculosis. *Health Lab Sci* 1978;**15**:38–43.
- 47 Christian P, West KP Jr. Interactions between zinc and vitamin A: An update. *Am J Clin Nutr* 1998;**68** (Suppl):435S–441S.
- 48 Mahalanabis D, Lahiri M, Paul D, Gupta S, Gupta A, Wahed MA, *et al*. Randomized, double-blind, placebo-controlled clinical trial of the efficacy of treatment with zinc or vitamin A in infants and young children with severe acute lower respiratory infection. *Am J Clin Nutr* 2004;**79**:430–6.
- 49 Lopez A. Malnutrition and the burden of disease. *Asia Pac J Clin Nutr* 2004;**13** (Suppl):S7.
- 50 Layton HW, Youmans GP. Effect of dietary factors upon the resistance of albino mice to experimental infection with *Mycobacterium tuberculosis*. *J Bacteriol* 1965;**90**:958–64.
- 51 Sklan D, Melamed D, Friedman A. The effect of varying levels of dietary vitamin A on immune response in the chick. *Poult Sci* 1994;**73**:843–7.
- 52 Jason J, Archibald LK, Nwanyanwu OC, Sowell AL, Buchanan I, Larned J, *et al*. Vitamin A levels and immunity in humans. *Clin Diagn Lab Immunol* 2002;**9**:616–21.
- 53 Albers R, Bol M, Bleumink R, Willems AA, Pieters RH. Effects of supplementation with vitamins A, C, and E, selenium, and zinc on immune function in a murine sensitization model. *Nutrition* 2003;**19**:940–6.
- 54 Iwata M, Eshima Y, Kagechika H. Retinoic acids exert direct effects on T cells to suppress Th1 development and enhance Th2 development via retinoic acid receptors. *Int Immunol* 2003;**15**:1017–25.
- 55 Crowle AJ, Ross EJ. Inhibition by retinoic acid of multiplication of virulent tubercle bacilli in cultured human macrophages. *Infect Immun* 1989;**57**:840–4.
- 56 Stephensen CB. Vitamin A, infection, and immune function. *Annu Rev Nutr* 2001;**21**:167–92.
- 57 Jason J, Buchanan I, Archibald L, Nwanyanwu OC, Bell M, Green TA, *et al*. Natural T, gamma delta and NK cells in mycobacterial, Salmonella, and human immunodeficiency virus infections. *J Infect Dis* 2000;**182**:474–81.
- 58 Chu CQ, Field M, Andrew E, Haskard D, Feldmann M, Maini RN. Detection of cytokines at the site of tuberculin-induced delayed-type hypersensitivity in man. *Clin Exp Immunol* 1992;**90**:522–9.
- 59 Tsiocopoulos A, Hamid Q, Varney V, Ying S, Moqbel R, Durham SR, *et al*. Preferential messenger RNA expression of Th1-type cells (IFN-gamma+, IL-2+) in classical delayed-type (tuberculin) hypersensitivity reactions in human skin. *J Immunol* 1992;**148**:2058–61.
- 60 Watson RR, Prabhala RH, Plezia PM, Alberts DS. Effect of beta-carotene on lymphocyte subpopulations in elderly humans: Evidence for a dose-response relationship. *Am J Clin Nutr* 1991;**53**:90–4.
- 61 Alexander M, Newmark H, Miller RG. Oral beta-carotene can increase the number of OKT4+ cells in human blood. *Immunol Lett* 1985;**9**:221–4.
- 62 Garewal HS, Ampel NM, Watson RR, Prabhala RH, Dols CL. A preliminary trial of beta-carotene in subjects infected with the human immunodeficiency virus. *J Nutr* 1992;**122** (3 Suppl):728–32.
- 63 Prabhala RH, Garewal HS, Hicks MJ, Sampliner RE, Watson RR. The effects of 13-cis-retinoic acid and beta-carotene on cellular immunity in humans. *Cancer* 1991;**67**:1556–60.
- 64 Santos MS, Meydani SN, Leka L, Wu D, Fotouhi N, Meydani M, *et al*. Natural killer cell activity in elderly men is enhanced by beta-carotene supplementation. *Am J Clin Nutr* 1996;**64**:772–7.
- 65 Aukrust P, Müller F, Ueland T, Svardal AM, Berge RK, Frøland SS. Decreased vitamin A levels in common variable immunodeficiency: Vitamin A supplementation *in vivo* enhances immunoglobulin production and downregulates inflammatory responses. *Eur J Clin Invest* 2000;**30**:252–9.
- 66 Hanekom WA, Hussey GD, Hughes EJ, Potgieter S, Yogev R, Check IJ. Plasma-soluble CD30 in childhood tuberculosis: Effects of disease severity, nutritional status, and vitamin A therapy. *Clin Diagn Lab Immunol* 1999;**6**:204–8.
- 67 Smith JC Jr, McDaniel EG, Fan FF, Halsted JA. Zinc: A trace element essential in vitamin A metabolism. *Science* 1973;**181**:954–5.
- 68 McMurray DN, Bartow RA, Mintzer CL, Hernandez-Frontera E. Micronutrient status and immune function in tuberculosis. *Ann N Y Acad Sci* 1990;**587**:59–69.