

# Interactions between zinc and vitamin A: an update<sup>1-4</sup>

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**ABSTRACT** Zinc status influences several aspects of vitamin A metabolism, including its absorption, transport, and utilization. Two common mechanisms postulated to explain this dependence relate to 1) the regulatory role of zinc in vitamin A transport mediated through protein synthesis, and 2) the oxidative conversion of retinol to retinal that requires the action of a zinc-dependent retinol dehydrogenase enzyme. However, evidence of an effect of zinc intake on vitamin A status from animal experiments is inconclusive, mainly because of the use of inadequate control groups. The higher weight gain of control animals as compared with the zinc-deficient ones in these experiments, even though pair fed, makes it difficult to isolate effects of zinc deficiency per se from those of generalized protein-energy malnutrition. A curvilinear relation has been suggested to describe an effect of plasma zinc on vitamin A transport. In humans, cross-sectional studies have more often than not shown a weak linkage between vitamin A and zinc status. Randomized trials have failed to show a consistent effect of zinc supplementation on vitamin A status. In disease states in which liver function is severely compromised and both zinc and vitamin A metabolism and transport are impaired, serum zinc and vitamin A concentrations tend to be positively correlated. In conclusion, clear evidence of synergy between these 2 micronutrients and its public health significance in humans is lacking. Research should focus on understanding this interaction in the context of coexisting moderate-to-severe zinc and vitamin A deficiencies in the population. *Am J Clin Nutr* 1998;68(suppl):435S-41S.

**KEY WORDS** Zinc, vitamin A, interactions, mechanisms, liver function, retinol binding protein, alcohol dehydrogenase

## INTRODUCTION

Zinc participates in the absorption, mobilization, transport, and metabolism of micronutrients, including vitamin A, most likely through its involvement in protein synthesis and cellular enzyme functions. There is also evidence that vitamin A affects zinc absorption and utilization. Thus, fluctuation in the status of one or both micronutrients may reasonably expect to alter the metabolism of the other, with functional consequences on the health of the individual. Whereas several studies have shown responses of vitamin A concentrations in plasma and liver to experimental zinc deficiency and repletion, earlier reviews found evidence of an interaction between these 2 micronutrients to be inconclusive (1, 2), mainly due to a failure of most animal studies to adequately control for the secondary effects of food and growth restriction that occur in zinc deficiency. Studies in

humans suggested that zinc supplementation favored vitamin A metabolism in some tissues when zinc deficiency was secondary to conditions such as alcoholic cirrhosis and other chronic liver diseases.

Two mechanisms are most often postulated to explain a potential dependence of vitamin A on zinc. One relates to a regulatory role of zinc on vitamin A transport mediated through protein synthesis (3, 4). Zinc deficiency can depress the synthesis of retinol-binding protein (RBP) in the liver and lead to lower concentrations of RBP in the plasma. Thus, reductions in plasma holo-RBP in animals fed zinc-deficient diets compared with their pair-fed, zinc-supplemented control counterparts may be due to impaired hepatic synthesis of the transport protein (5, 6), although partial food intake and growth restriction may confound this relation (6). The other postulated mechanism is an interaction between vitamin A and zinc through the ubiquitous, oxidative conversion of retinol to retinaldehyde (retinal), a critical step in the metabolic pathway of vitamin A that is well-described in the visual cycle in the retina of the eye (7) and requires the action of a zinc-dependent retinol dehydrogenase enzyme (8-9).

This review focuses on findings related to the interaction of zinc and vitamin A that have been reported since the earlier in-depth reviews to which readers are referred (1, 2), and attempts to assess the nutritional and public health significance of this interaction.

## ANIMAL STUDIES

Mechanisms postulated by which zinc may regulate vitamin A metabolism have focused on the control by zinc of RBP-mediated intercellular and intracellular transport of retinol and the role of zinc as a cofactor in the synthesis of enzymes that regulate vitamin A absorption and function. Earlier studies showed that the

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hepatic RBP synthesis required for mobilization of retinol from the liver is dependent on adequate zinc nutrition (1, 5). More recent experiments in rats also showed cellular hepatic RBP (cRBP) concentrations to be significantly reduced (by 50%) in zinc-deficient compared with pair-fed groups with adequate zinc intake in addition to having a lower serum retinol concentration (10). The findings suggest that zinc deficiency can impair transport of retinol to organelles within a cell and, thus, alter vitamin A metabolism before impairing transport of retinol via plasma RBP. However, the finding that control animals gained more weight than zinc-deficient animals despite pair feeding makes it difficult to isolate the effects of zinc deficiency per se from effects of the accompanying generalized malnutrition and protein deficiency on cRBP concentrations.

Another mechanism for the interaction between zinc and vitamin A was examined in an experiment in pair-fed rats on the changes in retinyl ester hydrolase and acyl CoA:retinol *O*-acyltransferase, hepatic enzymes that regulate retinyl ester hydrolysis as well as alcohol dehydrogenase (ADH) and retinal oxidase, which are necessary for the conversion of retinol to retinal and retinal to retinoic acid, respectively. Zinc deficiency did not change the retinyl ester hydrolase and acyl CoA:retinol *O*-acyltransferase activities. However, ADH activity declined significantly and retinal oxidase activity increased significantly in the zinc-deficient state (11). These changes in hepatic enzyme concentrations were accompanied by an increased concentration and total content of hepatic vitamin A, offering an alternative mechanism, other than possible reduction in RBP, for decreased metabolism of retinol in zinc deficiency. Increased retinal oxidase activity may be a compensatory response to maintain normal production of retinoic acid in the presence of decreased retinol degradation to its aldehyde. However, zinc-deficient rats also gained less weight than pair-fed control animals, again making it difficult to isolate the specific effects of zinc deficiency from general malnutrition and reduced growth in producing these enzyme changes.

Zinc may affect absorption of vitamin A. Zinc deficiency reduced lymphatic uptake of retinol in rats, which was attributed to a decrease in lymphatic phospholipid output resulting from impaired biliary secretion into the intestinal lumen (12). Enterocytes of zinc-deficient rats in another experiment failed to form chylomicrons, the principal carriers of dietary lipids including retinyl esters. Adding essential fatty acids to the diet did not counteract the adverse effect of zinc deficiency (13). These studies carefully controlled food intake, feeding patterns, and body weights in zinc-deficient, pair-fed control rats, suggesting that intestinal vitamin A malabsorption could be due to specific effects of zinc deficiency beyond any generalized effects of malnutrition.

Changes in vitamin A intake have effects on zinc absorption, status, and function. In situ experiments in vitamin-deficient chicks showed that zinc absorption was depressed not only throughout the small intestine (by 40%), but particularly in the ileum (by 57%) (14). Administration of retinyl acetate increased ileal absorption of zinc nearly 3-fold. Vitamin A-dependent synthesis of a protein in the ileal mucosa, which is putatively involved in binding zinc, was identified. It must be noted that experimental chicks manifested severe hypovitaminosis A; their body weight was 60% of that of the controls and they had secondary zinc deficiency. A dramatic decline in zinc absorption is likely to occur in severe vitamin A deficiency, although the

effects on zinc absorption of milder vitamin A deficiency remains unknown. In chicks fed a vitamin A-deficient diet, plasma zinc concentrations were lower (2.1 compared with 1.5  $\mu\text{g Zn}/10^6$  red blood cells) and hepatic zinc concentrations were higher ( $\approx 51$  compared with 62  $\mu\text{g Zn/g}$  liver) than vitamin A-adequate controls, effects that appeared to have been mediated through effects of vitamin A depletion on the activity of hepatic zinc-containing enzymes such as ADH, other hydrolytic enzymes, and superoxide dismutase (15).

### Interaction in pregnancy

The singular and joint effects of maternal zinc and vitamin A deficiencies on vitamin A status and pregnancy outcomes were examined in rats fed 3 different concentrations of zinc (100, 9, and 0.5  $\mu\text{g Zn/g}$ ) and vitamin A (400, 8, and 0  $\mu\text{g}\cdot\text{kg body wt}^{-1}\cdot\text{d}^{-1}$ ), representing adequate, marginally deficient, and deficient dietary concentrations, respectively, by using a factorial design (16). Marginal and deficient intakes of either zinc or vitamin A in dams and fetuses lowered plasma vitamin A concentrations compared with dams receiving adequate intakes of each nutrient. However, plasma retinol was lowest when vitamin A deficiency was accompanied by marginal-to-deficient concentrations of zinc in the diet, for which a strong statistical interaction was reported. There was also a tendency for hepatic vitamin A concentrations to increase with decreased dietary zinc, presumably reflecting impaired mobilization. Effects were observed in reproductive health outcomes. That is, the number of both implantation sites affected and malformed fetuses increased with marginal and deficient intakes of either vitamin A or zinc, but the consequences were more severe with combined deficiencies, also reflected by a statistical interaction between zinc and vitamin A with respect to both of these outcomes. However, only marginal and deficient intakes of zinc caused both maternal and fetal weight to decline, raising concern that dietary restriction and inanition may have been partly responsible for associated changes in vitamin A status and pregnancy outcomes. Subsequently, Peters et al (17), using a similar design and dietary zinc protocol, showed that supplemental dietary vitamin A given at high doses cannot ameliorate the deleterious effects of zinc deficiency on vitamin A metabolism during pregnancy. Pregnant rats were fed diets containing 100, 4.5, or 0.5  $\mu\text{g Zn/g}$  food and 4 (normal) or 8 (supplemental)  $\mu\text{g}$  retinyl acetate/g. Maternal plasma vitamin A concentrations decreased and liver vitamin A concentrations increased with zinc deficiency, which is indicative of decreased hepatic mobilization of vitamin A possibly from a lower rate of zinc-dependent RBP synthesis. Fetuses of zinc-deficient dams also had lower concentrations of plasma and liver vitamin A than control animals fed zinc-adequate diets. However, low intake of zinc in the diet also depressed maternal food intake, weight gain of dams, and fetal and placental weight gain and increased the incidence of birth defects, all influences that could partly obscure specific effects of zinc deficiency on maternal and fetal vitamin A status.

A study in pregnant rhesus monkeys suggested that marginal zinc deficiency may alter vitamin A metabolism by altering the formation or release of holo-RBP, or both, from the liver (18). Monkeys were fed either a zinc-sufficient (100  $\mu\text{g Zn/g}$ ) or a zinc-deficient (4  $\mu\text{g Zn/g}$ ) diet. Control animals were pair fed to the zinc-deficient group but were fed 100  $\mu\text{g Zn/g}$ . There was no difference in the circulating vitamin A and RBP concentrations of zinc-deficient and pair-fed pregnant controls during the third

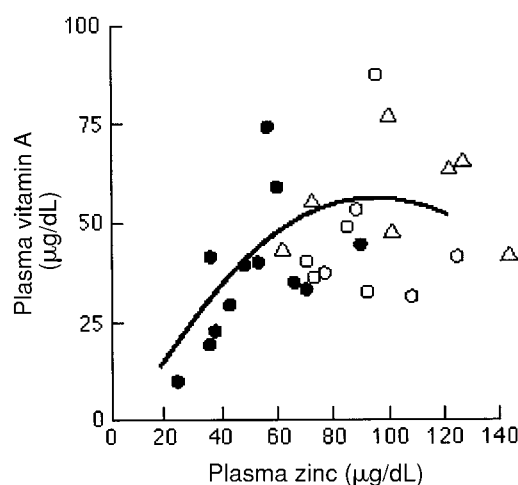
trimester. Neither was there a significant correlation between plasma concentrations of either vitamin A or RBP and zinc in the pair-fed and ad libitum-fed control groups. However, there was a strong correlation between plasma concentrations of vitamin A (Figure 1) and RBP with plasma zinc in the zinc-deficient groups, both at 135 d of pregnancy and at 3 mo postpartum. The authors concluded that above a certain threshold of plasma zinc, vitamin A transport is not dependent on plasma zinc concentration, but below that threshold vitamin A release and transport from the liver is strongly influenced by plasma zinc concentration. A polynomial regression equation that included a squared term for zinc provided the optimum fit for the curvilinear relation between plasma zinc and vitamin A (18). Similarly, a polynomial equation adequately fit the observed curvilinear relation between the maternal ratio of RBP to vitamin A and plasma zinc concentration, suggesting that the lowering effect of zinc deficiency on circulating retinol is mediated by reduced RBP synthesis and release from the liver.

### Interaction via the visual cycle

Animal data show that vitamin A and zinc interact during the conversion of retinol to retinal in the retina of the eye during the visual cycle (7), as well as in other tissues such as the liver and testes (9). The zinc metalloenzyme ADH is required for this oxidative process. Animal experiments and in vitro studies show that the retina is sensitive to zinc nutrition and that zinc deficiency can impair photoreceptor function by down-regulating ADH activity (8). Rhodopsin, a photosensitive pigment required for night vision, is synthesized from retinaldehyde and a membrane protein moiety, opsin. In zinc deficiency the formation of 13-*cis*-retinal is reduced, causing a decrease in rhodopsin formation and rod photosensitivity that can lead to poor dark adaptation or night blindness.

One study has questioned the role of impaired ADH activity in zinc deficiency-induced abnormal dark adaptation (19). Investigators measured the rate of rhodopsin regeneration in the following groups of rats: 1) zinc sufficient and ad libitum fed, 2) zinc deficient, and 3) zinc sufficient, pair fed, and weight matched. The initial rate of rhodopsin regeneration after 60 min of dark-adaptation, using the ocular concentration of 13-*cis*-retinal as an indicator, was not different among the 3 groups. After 120 min, the rhodopsin concentration was significantly higher in the ad libitum-fed group, but not in the zinc-deficient and pair-fed groups. These results did not suggest that zinc deficiency had caused the presumed reduction in ADH activity. Rather, generalized malnutrition that results from markedly reduced food intake may have depressed opsin synthesis (although unassessed) in the rod photoreceptor cells, which in turn may have lowered rhodopsin concentrations in the eyes.

Another study that examined electroretinogram changes in zinc and vitamin A deficiencies in rats showed that vitamin A deficiency could cause retinal degeneration that was not responsive to zinc (20). Vitamin A repletion, however, reversed the degeneration even in the presence of moderate zinc deficiency. At first, rats were deprived of both zinc and vitamin A. During a second phase they were randomized to receive either a vitamin A-deficient, zinc-deficient, or zinc- and vitamin A-sufficient diet. Retinograms of the zinc- and vitamin A-sufficient and zinc-deficient groups after 60 d were nearly normal, whereas the those of the vitamin A-deficient group showed deterioration, suggesting that retinal degeneration could be reversed with vita-



**FIGURE 1.** Relation between plasma vitamin A and zinc concentrations in rhesus monkeys at 135 d of pregnancy. ●, zinc-deficient; ○, food-restricted controls; △, ad libitum-fed controls. Conversion factors: for vitamin A, 1 µg/dL = 0.035 µmol/L; for zinc, 1 µg/dL = 0.153 µmol/L. Adapted from reference 18.

min A but not with zinc. The zinc- and vitamin A-sufficient group showed the greatest functional improvement but never reached the same level of function as a group of normal, continuously replete controls, indicating that some irreparable retinal damage occurred during the initial zinc- and vitamin A-depletion period.

### HUMAN STUDIES

Armed with evidence that zinc deficiency could affect vitamin A status and function (eg, by altering ADH-catalyzed conversions to intermediate retinoid forms or by reducing RBP synthesis), investigators studied interactions between zinc and vitamin A in humans, involving a variety of status, growth, and health indicators, in cross-sectional studies and single- or double-nutrient interventions (Table 1).

Cross-sectional studies have often failed to establish a consistent relation between vitamin A and zinc status; however, a positive association may exist in malnourished populations in which deficiencies of both micronutrients often coexist. In African children suffering from measles, serum zinc was significantly correlated with both serum vitamin A ( $r = 0.6$ ) and RBP ( $r = 0.7$ ) (25). Mean serum zinc concentrations were lower in school-aged Bangladeshi children with serum retinol concentrations  $<0.7$  µmol/L compared with those with concentrations  $>0.7$  µmol/L (26). A study of 3-9-y-old American children with delayed cognition observed a significantly lower serum vitamin A concentration in children with low serum zinc concentrations ( $<10.7$  µmol/L) than in children with higher circulating zinc concentrations (0.56 compared with 0.73 µmol/L) (23). On the other hand, no correlation was found between serum zinc and vitamin A concentrations in 102 growth-retarded (third percentile for height, weight, or head circumference) Mexican American migrant children (21). Children exhibiting normal growth were not included in the analysis. Also, no significant difference was observed in serum vitamin A concentration among pregnant teenagers of Mexican descent with low com-

**TABLE 1**  
Studies of zinc–vitamin A interactions in human populations<sup>1</sup>

Reference and year	Population	Interaction	Comment
Cross-sectional studies of association			
Chase et al (21), 1980	Mexican American migrant children <70 mo of age	No	No significant correlation between serum vitamin A and plasma zinc.
Hunt et al (22), 1985	Pregnant teenagers of Mexican descent	No	No differences observed in serum vitamin A concentrations between subjects with low and normal zinc status
Kozlowski et al (23), 1987	US children 3–9 y of age with delayed cognition	Yes	Serum RBP and vitamin A lower among children with serum zinc <10.7 μmol/L
Dorea et al (24), 1988	Fetuses and infants who died in the first 16 wk of life	No	Weak correlation between liver zinc and vitamin A concentrations
Coutsoudis et al (25), 1990	African children with measles	Yes	Baseline serum zinc concentrations correlated with vitamin A ( $r = 0.6$ ) and RBP ( $r = 0.7$ )
Ahmed et al (26), 1993	Bangladeshi children 5–12 y of age	Yes	Mean serum zinc concentrations lower among those with vitamin A concentrations <0.7 μmol/L
Supplementation trials			
Hunt et al (22), 1985	Low-income, pregnant teenagers of Mexican descent	No	Supplementation with zinc did not improve vitamin A status; maybe zinc was not limiting
Hustead et al (27), 1988	Preterm infants, birth weight <2000 g	Yes	Retinol and RBP values increased in zinc-supplemented group
Marinho et al (28), 1991	Brazilian children 3–7 y of age	Unknown	Data were not adequately compared
Udomkesmalee et al (29), 1992	Thai children 6–13 y of age	Weak support	Zinc supplementation did not improve vitamin A or RBP but improved dark adaptation time; vitamin A alone or with zinc did not improve vision but normalized conjunctival epithelium
Jalla et al (30), 1997	Indian children 5–36 mo of age	No	No effect of zinc on vitamin A status when given in addition to vitamin A

<sup>1</sup>RBP, retinol binding protein.

pared with acceptable zinc concentrations (22).

The few observational studies done to date are inconclusive with respect to a zinc–vitamin A status association during pregnancy. In Brazil, only a very weak and nonsignificant correlation was observed between liver zinc and vitamin A content of fetuses and stillborn infants ( $r = 0.2$ ) or infants who died in the first 4 mo of life ( $r = 0.14$ ) (24). In contrast, amniotic fluid and maternal serum concentrations of zinc and vitamin A were more highly correlated ( $r = 0.47$  and  $r = 0.32$ , respectively) in 106 British mothers, among whom were 12 women whose pregnancies were terminated for the presence of neural tube defects (31).

Supplementation intervention trials might be expected to clarify the presence and strength of an interaction between zinc and vitamin A. Hunt et al (22) randomly assigned pregnant Mexican teenagers to receive vitamin-mineral supplements with and without 20 mg Zn. Serum retinol concentrations, measured initially and later in pregnancy, did not change in either the zinc or placebo groups, indicating no effect of zinc supplementation on the vitamin A status of these girls. Serum retinol was relatively high in both groups (mean of  $\approx 1.85$  μmol/L), and it is unlikely that zinc status was limiting the maintenance of vitamin A status in this population. In another study, parasitized and nonparasitized children 3–7 y of age were randomly assigned to receive daily supplements of zinc (5 mg), vitamin A, both vitamin A and zinc, or placebo for 30 d (28). The daily dosage of vitamin A was specified erroneously as “500 mg” and may be 500 μg retinyl acetate instead. Retinol concentration was measured before and after supplementation. Serum retinol improved in all 4 groups without parasites, including the placebo group, making it diffi-

cult to infer any effect on serum retinol concentrations from either zinc or vitamin A supplementation. Serum retinol remained unchanged in all 4 groups with parasitic infection. In a group of 24 American preterm infants (with birth weight <2000 g), randomized intravenous zinc supplementation increased plasma retinol (by 0.32 μmol/L,  $P < 0.005$ ) and RBP (by 8 mg/L,  $P < 0.1$ ) over changes observed in placebo-treated control subjects, suggesting that zinc may have enhanced hepatic release of vitamin A through increased RBP production (27).

In **Table 2** are summarized the findings of one of the few population-based, double-masked, randomized trials examining the interaction between vitamin A and zinc supplementation in 6–13-y-old Thai children with marginal zinc and vitamin A deficiencies (29). Children were randomly assigned to receive either 25 mg Zn, 1500 retinol equivalents (RE) vitamin A, both zinc and

**TABLE 2**  
Effect of vitamin A and zinc supplementation on vitamin A status of Thai schoolchildren<sup>1</sup>

Treatment	Serum vitamin A	VRT	CIC
Vitamin A	↑	—	↑
Zinc	—	↑	↑
Vitamin A with zinc	↑	—	↑
Placebo	—	—	—

<sup>1</sup>VRT, visual restoration time; CIC, epithelial changes on the conjunctival surface obtained by using impression cytology; small arrows denote significant improvement ( $P < 0.05$ ); large arrows denote stronger significance ( $P < 0.01$ );  $n = 32$ –35/group. Data from reference 29.

vitamin A, or placebo daily for 6 mo. Outcome measures included serum retinol, zinc, and RBP concentrations, visual restoration time (VRT, a dark adaptation test), and epithelial changes on the conjunctival surface obtained by impression cytology (CIC). Whereas serum retinol concentration increased with vitamin A supplementation, zinc alone did not increase circulating concentrations of either vitamin A or RBP. VRT improved slightly in the group receiving zinc but not in any other group, indicating that zinc was more limiting than vitamin A with respect to scotopic vision in this population. Although the proportion of children with abnormal CIC results decreased significantly with either zinc or vitamin A, the conjunctival surface normalized in all initially CIC-abnormal children who received both zinc and vitamin A, revealing a possible synergism between zinc and vitamin A. Although only children with marginal zinc and vitamin A deficiencies were included in the trial, a lag time of 6–16 wk between screening and baseline assessment for enrollment showed an improvement in the circulating zinc and vitamin A concentrations in the subjects, which was attributed to seasonal increases in the availability of dietary zinc sources (29), although regression to the mean was also a likely factor. Thus, at entry into the trial, subjects had zinc and vitamin A statuses comparable with those of a normal population of US children.

A double-masked, randomized trial was carried out in India to evaluate the effects of daily zinc supplementation for 4 mo on the severity and duration of diarrheal morbidity in children 6–35 mo of age, all of whom were also provided a large dose of vitamin A at the outset (32). This design made it possible to examine the effect of zinc supplementation over that of vitamin A alone (control group) on serum retinol concentration. Findings showed that by the end of the trial, mean plasma retinol concentrations were similar in both groups (0.76  $\mu\text{mol/L}$  in the zinc-supplemented compared with 0.79 in the control group) (32) and comparable percentages of children in both groups had retinol concentrations  $<0.35 \mu\text{mol/L}$  (38% compared with 43%, respectively) (**Table 3**). Fifteen percent of children receiving vitamin A and zinc, but only 44% of those receiving vitamin A alone, had plasma retinol values of 0.35–0.70  $\mu\text{mol/L}$ . Conversely, a higher proportion of children receiving vitamin A alone had plasma retinol concentrations  $>1.05 \mu\text{mol/L}$  compared with those receiving zinc with vitamin A (15% compared with 7%). These complex shifts in plasma retinol indicated that there was little or no effect of zinc supplements on vitamin A status of the children. It is likely that increased zinc intake may only affect vitamin A status when children are moderately to severely protein-energy deficient, as has been observed before (33), or when children have low zinc status at the outset, but this needs to be examined.

#### ZINC-VITAMIN A INTERACTION IN DISEASE STATES

There may be an interaction between zinc and vitamin A in patients suffering from various pathologic conditions that severely compromise hepatic function such as alcoholic cirrhosis, cystic fibrosis, and idiopathic hemochromatosis. The nature and previous evidence of this interaction were reviewed by Solomons and Russell (2). Evidence of an interaction in the liver during chronic, and often wasting, disease states may provide clues to relevant interactions between these 2 nutrients in malnourished and ill populations.

The metabolism and transport of both zinc and vitamin A appear to be affected by chronic ethanol consumption and by the functional damage of hepatic cirrhosis. Several reports show an

**TABLE 3**

Effect on plasma vitamin A concentrations of supplementing children 6–35 mo of age with vitamin A and with zinc compared with vitamin A with placebo<sup>1</sup>

Plasma vitamin A concentration ( $\mu\text{mol/L}$ )	Vitamin A with zinc	Vitamin A with placebo
$\leq 0.35$	4 (4.4)	3 (3.2)
0.35–0.7	30 (33.3)	36 (38.3)
0.7–1.05	50 (56.6)	41 (43.6)
$> 1.05$	6 (6.7)	14 (14.9)

<sup>1</sup>n (%). Chi-square = 4.694,  $P = 0.261$ . Data from reference 30 and S Sazawal, R Black, unpublished observations, 1996.

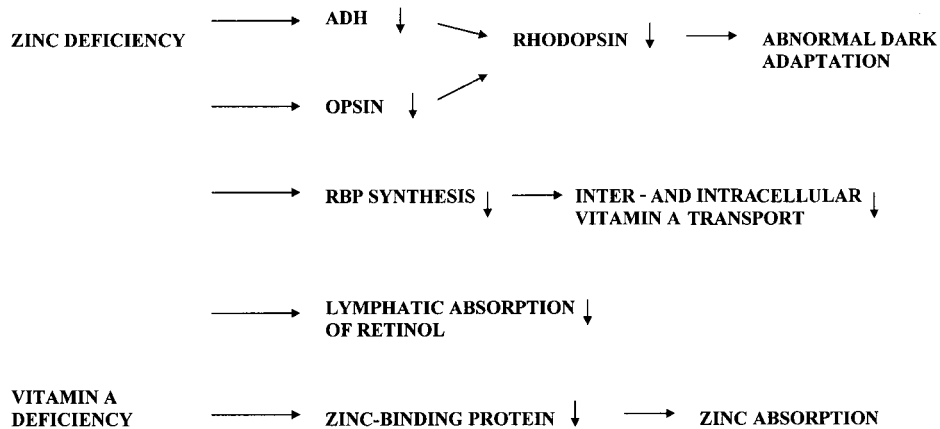
impairment in dark adaptation in alcoholic cirrhosis associated with deficiencies of zinc or vitamin A, or both (34–37). Liver cirrhosis can cause hypogonadism [which is also observed in zinc deficiency (38)], possibly because of depressed activity of zinc-dependent ADH that can also lead to lower testicular metabolism of retinol (9). Mean serum zinc and RBP concentrations were shown to be significantly lower in Nigerian cirrhotic patients with hypogonadism than in those without this condition (38). In alcoholics in Sri Lanka, serum concentrations of zinc and vitamin A were lower than in healthy control subjects (39). Serum zinc and vitamin A were positively correlated, but only in those with cirrhosis.

The presence of a zinc-vitamin A interaction was also explored in patients with cystic fibrosis, rheumatoid arthritis, and cancer of the larynx. Although Palin et al (40) showed no change in plasma vitamin A or RBP concentrations with zinc treatment in patients with cystic fibrosis, Navarro and Desquilbet (41) found that RBP was significantly lower in patients with cystic fibrosis and was positively correlated with plasma vitamin A concentrations. However, improved protein nutriture as a result of zinc supplementation could have caused the increase in plasma vitamin A concentrations (42). These studies regarding zinc-related vitamin A deficiency in cystic fibrosis are inconclusive.

Serum zinc concentrations were found to correlate positively with vitamin A and RBP concentrations in patients with cancer of the larynx, but not in patients with other nonmalignant laryngeal diseases (43). It was postulated that a rapidly growing tumor can increase the body's requirement for zinc, causing a reduction in the circulating concentrations of zinc that could depress zinc-dependent hepatic RBP synthesis and, consequently, lower plasma retinol. A similar explanation has been offered for the hypovitaminosis A observed in patients with rheumatoid arthritis (44). Associations between circulating zinc and vitamin A concentrations in disease states may reflect direct effects of one nutrient (or its relative absence) on the other; however, concurrent deficiencies of other nutrients, especially protein, may also explain these apparent interactions.

#### CONCLUSION


Absorption, metabolism, hepatic release, transport, and tissue utilization of vitamin A may depend, in part, on adequate zinc status. Circulating and hepatic concentrations of retinol have been observed to decline and rise in experimental zinc deficiency and repletion, respectively, in animals fed adequate amounts of vitamin A, although effects of food restriction have often not been adequately controlled for. In **Figure 2** the potential mecha-



**FIGURE 2.** Potential mechanism for zinc and vitamin A interaction. ADH, alcohol dehydrogenase; RBP, retinol binding protein.

nisms whereby zinc and vitamin A may interact are summarized. Zinc appears to regulate the metabolic conversion of retinol to retinal, an enzymatic step requiring zinc-dependent ADH, in the intestine, liver, testes, and in the retina, where it participates in an essential step of the visual cycle. Zinc deficiency may also impair synthesis of the protein opsin. Zinc is required for hepatic synthesis of cRBP and RBP, implying a regulatory role for zinc in mobilizing vitamin A within cells and from the liver. Conversely, severe vitamin A deficiency may reduce absorption and lymphatic transport of zinc by altering synthesis of a zinc-dependent binding protein. In mammals and humans, circulating zinc and vitamin A concentrations appear unrelated in well-nourished states but tend to co-vary in marginally nourished individuals with coexisting zinc and vitamin A deficiencies.

These observations suggest that zinc deficiency could both precipitate health consequences associated with both zinc deficiency and, through its gatekeeping roles, impose a secondary vitamin A deficiency in human populations. Furthermore, zinc supplementation of marginally nourished groups might be expected to improve indicators of both zinc and vitamin A status and associated health outcomes. Zinc deficiency might also be expected to limit the health and nutritional effect of vitamin A interventions, eg, on the occurrence of night blindness in a population. Although vitamin A deficiency could also interfere with zinc efficacy, data are more sparse to support this interaction. These, however, remain theoretical concerns. Clear evidence of amplified health consequences resulting from joint deficiencies or restricted health and nutritional benefits of vitamin A in the absence of zinc interventions in humans is lacking. The few trials conducted in malnourished populations show inconsistent responses in indicators of vitamin A or zinc status when the other nutrient is introduced. Further, vitamin A interventions in the absence of zinc supplementation were highly effective in dramatically reducing night blindness and other forms of xerophthalmia, anemia, the severity of infectious morbidity, and mortality rates of young children (45) in populations in which zinc deficiency could have been expected to be prevalent. However, this does not rule out even greater potential effects of vitamin A in the presence of adequate zinc nutriture. Lack of evidence about the public health effect of a potential zinc-vitamin A interaction on health and disease, given the critical roles played by each individual nutrient in main-

taining resistance to infection, should stimulate greater effort to address this issue in the future. 

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