



## INTERACTION OF VIT-A AND ZINC IN ANIMAL NUTRITION

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**ABSTRACT**

Evidence of an effect of zinc intake on vitamin A status from animal experiments is inconclusive, mainly because of the utilization of inadequate control groups. The higher weight gain of control animals as compared with the zinc-deficient ones in these experiments, even though pair victualled, makes it arduous to isolate effects of zinc deficiency per se from those of generalized protein-energy malnutrition. A curvilinear cognation has been suggested to describe an effect of plasma zinc on vitamin A convey. In animals, cross-sectional studies have more often than not shown an impotent linkage between vitamin A and zinc status. Randomized tribulations have failed to show a consistent effect of zinc supplementation on vitamin A status. In disease states in which liver function is astringently compromised and both zinc and vitamin A metabolism and convey are impaired, serum zinc and vitamin A concentrations incline to be positively correlated. In conclusion, clear evidence of synergy between these 2 micronutrients and its public health paramountcy in animals is destitute. Research should fixate on understanding this interaction in the context of coexisting moderate-to-astringent zinc and vitamin A deficiencies in the population.

**KEYWORDS:** Zinc, vitamin A, interactions, mechanisms, liver function, retinol binding protein, alcohol dehydrogenase.

**INTRODUCTION**

Zinc participates in the absorption, mobilization, convey, and metabolism of micronutrients, including vitamin A, most likely through its involution in protein synthesis and cellular enzyme functions. There is additionally evidence that vitamin A affects zinc absorption and utilization. Thus, fluctuation in the status of one or both micronutrients may plausibly expect to alter the metabolism of the other, with functional consequences on the health of the individual. Whereas several studies have shown replications 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 (Smith, 1980; Solomons, 1980; Mejia, 1986), mainly due to a failure of most animal studies to adequately control for the secondary effects of aliment and magnification restriction that occur in zinc deficiency. Studies in animals 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 expound a potential dependence of vitamin A on zinc. One relates to a regulatory role of zinc on vitamin A convey mediated through protein synthesis (Terhone *et al.*, 1972; Smith *et al.*, 1974, 1976; Wald, 1950). Zinc deficiency can dispirit 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 alimented zinc-deficient diets compared with their dyad-alimented, zinc-supplemented control

counterparts may be due to impaired hepatic synthesis of the convey protein (Huber and Gershof, 1975; Sundaresan *et al.*, 1977), albeit partial victuals intake and magnification restriction may confound this cognation (Mobarhan *et al.*, 1992; Boron *et al.*, 1988; Ahn and Koo, 1995). 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 ocular perceiver (Berzin and Baoman, 1987) and requires the action of a zinc-dependent retinol dehydrogenase enzyme (Sklan *et al.*, 1987; Duncan *et al.*, 1978).

**Livestock studies**

Mechanisms postulated by which zinc may regulate vitamin A metabolism have fixated on the control by zinc of RBP-mediated intercellular and intracellular convey 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 hepatic RBP synthesis required for mobilization of retinol from the liver is dependent on adequate zinc nutriture (Peters *et al.*, 1986; Baly *et al.*, 1984; Dorea and Olson, 1986). More recent experiments in rats additionally showed cellular hepatic RBP (cRBP) concentrations to be significantly reduced (by 50%) in zinc-deficient compared with pair-alimented groups with adequate zinc intake in integration to having a lower serum retinol concentration (Kraft *et al.*, 1987). The findings suggest that zinc deficiency can impair convey of retinol to organelles within a cell and, thus, alter vitamin A metabolism afore impairing convey of retinol via plasma

RBP. However, the finding that control animals gained more weight than zinc-deficient animals despite pair victualing makes it arduous 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-alimented rats on the transmutations 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 indispensable for the conversion of retinol to retinal and retinal to retinoic acid, respectively. Zinc deficiency did not transmute the retinyl ester hydrolase and acyl CoA: retinol O-acyltransferase activities. However, ADH activity declined significantly and retinal oxidase activity incremented significantly in the zinc-deficient state (Chase *et al.*, 1980). These vicissitudes in hepatic enzyme concentrations were accompanied by an incremented concentration and total content of hepatic vitamin A, offering an alternative mechanism, other than possible reduction in RBP, for decremented metabolism of retinol in zinc deficiency. Incremented retinal oxidase activity may be a compensatory replication to maintain mundane engenderment of retinoic acid in the presence of decremented retinol degradation to its aldehyde. However, zinc-deficient rats additionally gained less weight than pair-victualled control animals, again making it arduous to isolate the categorical effects of zinc deficiency from general malnutrition and reduced magnification in engendering these enzyme changes. Zinc may affect absorption of vitamin A. Zinc deficiency reduced lymphatic uptake of retinol in rats, which was attributed to a decrementation in lymphatic phospholipid output resulting from impaired biliary secretion into the intestinal lumen (Hunt *et al.*, 1988; Kozłowski *et al.*, 1987; Dorea and Araujo, 1988). Enterocytes of zinc-deficient rats in another experiment failed to compose chylomicrons, the principal carriers of dietary lipids including retinyl esters. Integrating essential adipose acids to the diet did not counteract the unpropitious effect of zinc deficiency (Coutsoudis *et al.*, 1993). These studies conscientiously controlled pabulum intake, alimending patterns, and body weights in zinc-deficient, pair-alimented control rats, suggesting that intestinal vitamin A malabsorption could be due to categorical effects of zinc deficiency beyond any generalized effects of malnutrition. Transmutations in vitamin A intake have effects on zinc absorption, status, and function. In situ experiments in vitamin-deficient chicks showed that zinc absorption was dispirited not only throughout the diminutive intestine (by 40%), but categorically in the ileum (by 57%) (Ahmed *et al.*, 1993). 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 astringent 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 liable to occur in rigorous vitamin A deficiency, albeit the effects on zinc absorption of milder vitamin A deficiency remain unknown. In chicks

alimented a vitamin A-deficient diet, plasma zinc concentrations were lower (2.1 compared with 1.5 mg Zn/10<sup>6</sup> red blood cells) and hepatic zinc concentrations were higher (<51 compared with 62 mg 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 (Hustead *et al.*, 1988; Marihno *et al.*, 1991; Udomkesmalee *et al.*, 1992). 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 vigorous statistical interaction was reported. There was additionally a proclivity for hepatic vitamin A concentrations to increment with decremented dietary zinc, presumably reflecting impaired mobilization. Effects were observed in reproductive health outcomes. That is, the numbers of both implantation sites affected and malformed fetuses incremented with marginal and deficient intakes of either vitamin A or zinc, but the consequences were more rigorous with amalgamated deficiencies, withal reflected by a statistical interaction between zinc and vitamin A with reverence 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 vicissitudes in vitamin A status and pregnancy outcomes. Subsequently, Peters *et al.* (Parkinso *et al.*, 1982), utilizing a kindred 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. Enceinte rats were victualled diets containing 100, 4.5, or 0.5 mg Zn/g pabulum and 4 (mundane) or 8 (supplemental) mg retinyl acetate/g. Maternal plasma vitamin A concentrations decremented and liver vitamin A concentrations incremented with zinc deficiency, which is indicative of decremented hepatic mobilization of vitamin A possibly from a lower rate of zinc-dependent RBP synthesis. Fetuses of zinc deficient dams additionally had lower concentrations of plasma and liver vitamin A than control animals alimented zinc-adequate diets. However, low intake of zinc in the diet withal dejected maternal pabulum intake, weight gain of dams, and fetal and placental weight gain and incremented the incidence of birth defects, all influences that could partly obscure concrete effects of zinc deficiency on maternal and fetal vitamin A status. A study in enceinte rhesus monkeys suggested that marginal zinc deficiency may alter vitamin A metabolism by altering the formation or relinquishment of holo-RBP, or both, from the liver (Sazawal *et al.*, 1999). Monkeys were alimented either a zinc-sufficient (100 mg Zn/g) or a zinc-deficient (4 mg Zn/g) diet. Control animals were pair victualled to the zinc-deficient group but was alimented 100 mg Zn/g. There was no difference in the circulating vitamin A and RBP concentrations of zinc-deficient and pair-victualled enceinte controls during the third trimester.

Neither was there a paramount correlation between plasma concentrations of either vitamin A or RBP and zinc in the dyad-alimented and ad libitum-fed control groups. However, there was a vigorous correlation between plasma concentrations of vitamin A. The authors concluded that above a certain threshold of plasma zinc, vitamin A convey is not dependent on plasma zinc concentration, but below that threshold vitamin A relinquishment and convey from the liver is vigorously influenced by plasma zinc concentration. A polynomial regression equation that included a squared term for zinc provided the optimum fit for the curvilinear cognation between plasma zinc and vitamin A (Shingwekar *et al.*, 1979; Patek and Haig, 1939; Russeii *et al.*, 1978). Similarly, a polynomial equation adequately fit the observed curvilinear cognation between the maternal ratios. The authors concluded that above a certain threshold of plasma zinc, vitamin A convey is not dependent on plasma zinc concentration, but below that threshold vitamin A relinquishment and convey from the liver is vigorously influenced by plasma zinc concentration. A polynomial regression equation that included a squared term for zinc provided the optimum fit for the curvilinear cognation between plasma zinc and vitamin A (Morrison *et al.*, 1978). Similarly, a polynomial equation adequately fit the observed curvilinear cognation 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 relinquish from the liver. Animal data show that vitamin A and zinc interact during the conversion of retinol to retinal in the retina of the ocular perceiver during the visual cycle (Meclain *et al.*, 1979), as well as in other tissues such as the liver and testes (Abdo-gusua *et al.*, 1989). The zinc metalloenzyme ADH is required for this oxidative process. Animal experiments and in vitro studies show that the retina is sensitive to zinc nutriture and that zinc deficiency can impair photoreceptor function by down-regulating ADH activity (Atukorala *et al.*, 1986). 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 decrementation in rhodopsin formation and rod photosensitivity that can lead to poor dark adaptation or night optical incapacitation. One study has queried the role of impaired ADH activity in zinc deficiency-induced eccentric dark adaptation (Plain *et al.*, 1973; Navarro *et al.*, 1981; Underwood *et al.*, 1981). Investigators quantified the rate of rhodopsin regeneration in the following groups of rats: 1) zinc sufficient and ad libitum victualed, 2) zinc deficient, and 3) zinc sufficient, pair victualed, and weight matched. The initial rate of rhodopsin regeneration after 60 min of dark-adaptation, utilizing the ocular concentration of 13-cisretinal as a designator, 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-alimented groups. These results did not suggest that zinc deficiency had caused the postulated reduction in ADH activity. Rather, generalized malnutrition that results from markedly reduced victuals

intake may have dejected opsin synthesis (albeit unassessed) in the rod photoreceptor cells, which in turn may have lowered rhodopsin concentrations in the ocular perceivers. Another study that examined electroretinogram vicissitudes in zinc and vitamin A deficiencies in rats showed that vitamin A deficiency could cause retinal degeneration that was not responsive to zinc (Drodo *et al.*, 1989; Honaker *et al.*, 1989; Sommer *et al.*, 1996). Vitamin A repletion, however, inverted 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 proximately mundane, whereas the those of the vitamin A-deficient group showed deterioration, suggesting that retinal degeneration could be inverted with vita min A but not with zinc. The zinc- and vitamin A-sufficient group showed the greatest functional amendment but never reached the same level of function as a group of mundane, perpetually replete controls, designating that some irreparable retinal damage occurred during the initial zinc- and vitamin A-depletion period.

## CONCLUSION

Absorption, metabolism, hepatic release, convey, and tissue utilization of vitamin A may depend, in part, on adequate zinc status. Zinc deficiency may withal impair synthesis of the protein opsin. Zinc is required for hepatic synthesis of cRBP and RBP, implicatively insinuating a regulatory role for zinc in mobilizing vitamin A within cells and from the liver. Conversely, rigorous vitamin A deficiency may reduce absorption and lymphatic convey of zinc by altering synthesis of a zincdependent binding protein. In mammals and animals, circulating zinc and vitamin A concentrations appear unrelated in well-victualed states but incline to co-vary in marginally alimented 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 animal populations. Furthermore, zinc supplementation of marginally victualed groups might be expected to amend designators of both zinc and vitamin A status and associated health outcomes. Zinc deficiency might withal be expected to inhibit the health and alimantal effect of vitamin A interventions, eg, on the occurrence of night optical incapacitation in a population. Albeit vitamin A deficiency could withal interfere with zinc efficacy, data are more sparse to fortify this interaction. These, however, remain theoretical concerns. Clear evidence of amplified health consequences resulting from joint deficiencies or restricted health and alimantal benefits of vitamin A in the absence of zinc interventions in animals is destitute. The few tribulations conducted in malnourished populations show inconsistently erratic replications in bespeakers of vitamin A or zinc status when the other nutrient is introduced. Further, vitamin A interventions in the absence of zinc supplementation were highly efficacious in dramatically reducing night visual

impairment and other forms of xerophthalmia, anemia, the rigor of infectious morbidity, and mortality rates of puerile children in populations in which zinc deficiency could have been expected to be prevalent. However, this does not rule out even more preponderant potential effects of vitamin A in the presence of adequate zinc nutrition. 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 staining resistance to infection, should stimulate more preponderant effort to address this issue in the future.

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