Possible Role of Zinc in Vitamin A Nutritional Status

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SUMMARY

In summary, although nemerous studies in different animal species and humans have provided evidence for an essential role of zinc in vitamin A metabolism, there remains a need for well-control double-blind intervention studies. Ideally, the investigations would involve subjects free of chronic diseses without severe malnutrition. In addition, the subjects should exhibit suboptimal status of both zinc and vitamin A. The impaired nutriture should first be documented by a combination of biochemical and functional parameters. Preliminary survey in NE Thailand indicates a prevalence of combined inadequacies of both zinc and vitamin A, a result of insufficient dietary intake of these nutrients.

Therefore, the definitive data obtained from the proposed study could be used for the implementaion of the community nutrition education program as well as the expansion of public health effort to assure the eradication of zinc and vitamin A deficiencies among the population at risk. The results should be applicable to children in other developing countries if their zinc and/or vitamin A status is less than optimal.

INTRODUCTION

In recent years, there has been a growing interest in the area of nutrient interactions, particularly, the functional consequences of combined deficiencies. Increasing attention has been focused on a possible role of zinc in vitamin A metabolism. Data are accumulating in experimental animals and humans supporting the concept that inadequate zinc nutriture may result in an impairment of vitamin A status.

I. Thailand conditions

Vitamin A Nutriture

The role of vitamin A in epithelial cell differentiation, vision, and reproduction is well established[1]. The widespread occurrence of vitamin A deficiency which can lead to severe eye lesions and blindness has been recognized globally within the last twenty five years. Recently, it has been estimated that a minimum of one-quarter million children in Asia become blind yearly from severe corneal xerophthalmia with an additional five million suffering from a milder form of the disease[2]. In Thailand, a 1960 ICNND survey reported inadequate dietary intakes of vitamin A and indicated that vitamin A malnutrition was evident among the infants and small children in the North and the Northeast regions[3]. The Fourth National Food and Nutrition Development Plan of Thailand for the period 1977–81 recognized vitamin A malnutrition as one of the seven national nutritional problems.

Dietary survey data collected by the Institute of Nutrition at Mahidol University in 1967 indicated that vitamin A intakes of the Northeast villagers were only one-third the amount consumed by those living in towns. The intakes in both groups were below the US recommended dietary allowances (RDA). A later survey in 1973 of the dietary nutrient intake of preschool children in Ubon province in NE Thailand revealed that the average vitamin A intake was only one tenth to one half the RDAs[4], as shown in Table 1. In addition, fat intake was extremely low and contributed only 3–5% of daily energy intake. A recent dietary survey carried out in January of 1987 (Table 2), included preschool children, pregnant women and lactating mothers residing in rural areas of Ubon and Srisaket. The data reveal vitamin A intakes of 42, 39 and 31% respectively of the US recommendations (Dhanamitta et al., unpublished data 1987). Thus, marginal intakes of vitamin A remain prevalent among the inhabitants of specific regions of NE Thailand.

A biochemical study which measured serum vitamin A concentrations in young children and lactating mothers of Northeast villages during 1974 to 1978 identified vitamin A deficiency as a public health problem (Table 3). Seventeen percent of preschool children and 22% of the school-aged children exhibited serum vitamin A of less than 10 μg/dl, a level considered to indicated overt deficiency. Likewise low serum vitamin A concentrations were noted in 42% of lactating mothers[4]. A recent study involving the analysis of serum vitamin A concetrations of 225 rural school children of these regions indicated that only 1.3% of these children showed serum values of less than 10 μ/dl. A marginal range of serum vitamin A concentrations (10–20 μg/dl) was observed in 11.1% of the children (Dhanamitta, et al. unpublished data 1987). In addition, our preliminary survey revealed an impaired dark adaptation in 11% of these children. Since the preschool children represent a high-risk group for nutrient deficiencies, a higher incidence is expected than for older children or adults. Altnough recent data would indicate that a considerable proportion of village children exhibit suboptimal vitamin A status, the severity of the problem has declined, indicating improved vitamin A nutriture duirng the past decade.

Zinc Nutriture

Zinc is essential for normal growth and development in man and animals. The first observation of human zinc deficiency was reported from the Middle East in early 1960's and later in the United States[5]. Zinc deficient subjects exhibit severely impaired growth, delayed sexual maturation, poor appetite, and low plasma and hair zinc concentrations[6]. Etiological factors associated with zinc deficiency in humans include: 1) Low bioavailability of zinc from cereal-based, low-meat diets typically consumed in Asia and Middle-East countries 2) Loss of zinc via sweat in hot climates and 3) Geophagia[7] (clay-eating habit). All of these factors are present in Northeast Thailand. The major dietary items consumed by the villagers of these regions included glutinous rice, fermented fish, fish (dried or grilled), vegetables and chilis. The estimated daily zinc intake in the school children of this region is 5 mg compared to the US RDA of 10 mg for a similar age group. Recent data from 283 school children in Ubon and Srisaket provinces, Northeast Thailand reveal an incidence of 70% with low serum Zinc (<70 μg/dl) (Udomkesmalee and Dhanamitta, unpublished data 1987). An earlier

Table 1. Average dietary nutrient intake per person per day in preschool children (Posai, Ubon, N. E., Thailand 1973)

Ages years	No. of Subjects	Energy K Cal	CHO Percentage of Calories	Fat Percentage of Calories	Protein Percentage of Calories	Vit. A μg retirol equivalents
2	3	806	84	3.3	11	63
3	8	935	86	3.6	10	206.4
4	11	1,078	88	4.8	11	252.6
5	10	1,089	84	4.0	11	178.8
6	11	1,149	84	4.9	11	326.4
RDA*	–	1,200–1,800	50–80	25–35	15	600–750

*Recommended Dietary Allowance, Food and Nutrition Board, 8th Revised Edition, Natl. Acad. Sci.—Natl. Res. Council, Washington, D. C., 1974.

Table 2. Dietary vitamin A intake in Ubon & Srisaket Provinces, N. E., Thailand, 1987

Subject	n	x̄ ± SE (μg RE)	US-RDA 1980 (μg RE)	% RDA
Children (2–5 yrs old)	171	195 ± 20	400–500	42
Pregnant Women	61	376 ± 45	1000	39
Lactating Mothers	87	367 ± 40	1200	31

Table 3. Serum vitamin A levels in preschool children, school children and lactating mothers (Ubon, N. E., Thailand, 1974 and 1978)

Level of Serum Vit. A (μg/dl)	Preschool children		School children		Lactating Mother	
	No. of subjects	Percent	No. of subjects	Percent	No. of subjects	Percent
Deficient (<10)	25	17	15	22	1	2
Marginal (10–20)	102	70	34	51	18	42
Adequate (>20)	19	13	18	27	24	56
Mean ± SE	15 ± 0.7		16 ± 1.2		23 ± 1.2	
Total Subjects	146	100	67	100	43	100

study[8] involving well-nourished children in Bangkok indicated a mean serum zinc concentraiton of 88 ±9 μg/dl which is similar to the level reported for US children of approximately the same age.[9] Recent analysis of serum vitamin A and zinc concentrations from rural school children residing in Ubon and Srisaket Provinces suggest that approximately one out of four may be at risk for Vitamin A and Zinc deficiencies (Udomkesmalee and Dhanamitta, unpublished data 1987).

II. Zinc and vitamin A interaction: A review

It is well established that nutrient interactions exist among several vitamins and minerals including vitamin D and calcium, vitamin C and iron and selenium and vitamin E. Recently, data supporting the concept of interaction between zinc and vitamin A have been accumulating. In retrospect, several early studies involving both animals and humans as well as *in vitro* observations suggested a role of zinc in vitamin A metabolism. In 1939, Patek and Haig reported that 19 out of 24 patients with liver cirrhosis showed abnormal dark adaptation despite sufficient intake of vitamin A. Furthermore, certain patients were apparently resistant to therapy of massive doses of vitamin A[10]. Later Vallee *et al*[11] suggested that the resistance to therapy in some of the cirrhotics might have been due to the altered zinc metabolism associated with that condition. Stevenson and Earle[12] observed that zinc-deficient swine had low plasma vitamin A which was also unresponsive to large doses of vitamin A supplementation. Other animal studies using ruminants also showed low serum vitamin A concentrations when fed a zinc-deficient, vitamin A–adequate diet. Furthermore zinc supplementation increased the efficacy of vitamin A therapy[13,14]. Other data[15] supporting the interaction of two nutrients include the revelation that the enzyme, alcohol dehydrogenase, invovled in vitamin A metabolism, is zinc-dependent. In addition, the retina, an active site of vitamin A function in vision, contains the highest tissue concentrations of zinc in the body[16].

In a series of experiments by Smith and colleagues[17], employing rats that were deficient in both zinc and vitamin A, they demonstrated that zinc was necessary for the mobilization of vitamin A from the liver to the plasma. This was indicated by low plasma vitamin A despite adequate liver stores in the zinc-deficient animals, suggesting an impaired ability to mobilize vitamin A. At that time they speculated that zinc may be involved in the synthesis of function of retinol binding protein or RBP. In a second series of experiments[18], RBP was shown to be significantly depressed in the liver and plasma of the zinc-deficient animals compared to pair-fed controls. It was suggested that zinc deficiency impairs the synthesis of RBP in the liver. In the only study [19] involving pregnant primates with marginal zinc deficiency, a positive correlation existed between plasma zinc and both plasma vitamin A and RBP. The authors suggested that marginal zinc status may alter vitamin A metabolism.

Smith and coworkers[20,21] reported that a high percentage of alcoholic liver disease patients exhibited both low plasma zinc and vitamin A and call attention to a pssible interrelationship among liver disease, zinc, vitamin A and retionol-binding protein. Later, Morrison *et al.*[22] studied six alcoholic cirrhotics who had abnormal darkadaptation and low serum zinc concentrations. Zinc therapy corrected the impaired dark adaptation in five out of six patients with the sixth one showed an improvement. In an expanded study from the same laboratory with a larger number of subjects, the results confirmed the beneficial effect of zinc therapy on impaired dark adaptation in alcoholic cirrhotics[23]. McClain *et al.*[24] reported that zinc therapy normalized the abnormal dark adaptation of alcoholic cirrhosis patients who were resistant to vitamin A supplementation alone. In contrast, Weismann *et al.*[25] in a double blind study failed to confirm the effect of zinc supplementation on vitamin A nutriture including serrum concentrations and dark adaptation. Only one out of 30 patients exhibited impaired dark adaptation. However, baseline plasma zinc concentrations of these subjects were within the normal range. Likewise, other studies[26,27] involving patients with normal zinc status as indicated by serum or plasma concentrations within normal range have failed to improve indices of vitamin A nutriture.

A report from India involving protein-energy malnourished children with low plasma zinc concentrations demonstrated a response to short-term zinc supplementation by raising plasma vitamin A and RBP[28].

Therefore, a limited number of human studies suggest that zinc supplementation may be beneficial in conditions where zinc nutriture is inadequate. However, more definitive studies involving nutritional zinc deficiency in humans are necessary to establish the indispensable role of zinc in vitamin A metabolism.

III. Future research

It appears that the conditions necessary to test the hypothesis that zinc is required for normal vitamin A nutriture in humans are prevalent in Northeast Thailand. Recent data collected from children residing in Ubon and Srisaket Provinces indicate that a high proportion of these children are apparently at risk for suboptimal zinc and vitamin A nutriture as indicated by low dietary intake and plasma concentrations of both nutrients as well as impaired visual function. Therefore, we propose a double-blind supplementation study involving school children who exhibit suboptimal zinc and vitamin A statuses. The parameters to be measured include biochemical and functional assessments. The biochemical indices include plasma zinc, vitamin A and RBP as well as hair zinc concentrations. Functional tests include dark adaptaiton, impression cytology, immune-response and growth. One hundred and twenty children, matched for age and sex will be assigned to one of four treatments i.e. placebo, vitamin A, zinc and vitamin A plus zinc. Parameters of zinc and vitamin A will be determined at 0, 3 and 6 months after supplementation.

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