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TROPICAL AND GEOGRAPHICAL MEDICINE

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Chapter 122

Zinc

Noel W. Solomons, Roger Shrimpton

NUTRIENT

SOURCES OF ZINC IN THE DIET

Zinc is an essential trace element in human nutrition. Recommended dietary allowance (RDA) for daily zinc intake of healthy individuals in the United States according to age and sex is: 0 to 6 months, 3 mg; 6 to 12 months, 5 mg; 1 to 10 years, 10 mg; adolescents, adult men, and nonpregnant women, 15 mg; pregnant women, 20 mg; and lactating mothers, 25 mg [*1*]. However, surveys in the United States indicate that most individuals receive only 45 to 70 percent of the RDA. The zinc density of most self-selected diets is such that the RDA for zinc will not be ingested when energy requirements are met, as most common, basic staple foods contain less than the approximate 5 mg per 1000 kcal necessary to satisfy the RDA. A satisfactory daily intake thus depends on consuming zinc-rich foods such as nuts and whole grains, pork, poultry, milk, low-fat cheeses, yogurt, eggs (7 to 12 mg zinc per 1000 kcal), and/or very zinc-rich foods such as leafy and root vegetables, crustacea, beef, kidney, liver, heart, and mollusks (containing > 12 mg zinc per 1000 kcal) [*2*] (see Table 122-1).

A number of dietary substances affect the biological availability of zinc. Plant components, primarily dietary fiber and phytins, are major inhibitors of zinc absorption, although dietary protein levels also exert an influence [*3*]. Dietary staples in some areas of the world are rich in phytin and fiber, such as the whole-wheat flatbread of Iran, *tanok*, and the traditional corn tortillas of southern Mexico and Central America. Oxalates from leafy vegetables, tannins in sorghum and tea, and excessive iron-zinc ratios also interfere with the absorption of dietary zinc [*4*].

Table 122-1. Classification of dietary zinc sources based on nutrient-energy density*

Zinc category, mg/1000 kcal	Foods
Very poor 0–2	Fats, oils, butter, cream cheese, sweets, chocolates, soft drinks, alcoholic drinks, sugars, jams, and preserves
Poor 1–5	Fish, fruits, refined cereal products, pastries, biscuits, cakes, puddings, tubers, plantains, sausages, chips
Rich 4–12	Whole grains, pork, poultry, milk, low-fat cheese, yogurt, eggs, nuts
Very rich 12–882	Lamb, leafy and root vegetables, crustacea, beef, kidney, liver, heart, mollusks

*Calculated from data in Ref. 2.

PHYSIOLOGY

Zinc apparently can be absorbed at all levels of the small intestine. Dietary zinc incorporated into organic molecules must be digested free of its protein matrixes before becoming available for absorption. Meal-stimulated pancreatic secretion delivers an amount of zinc into the duodenum equivalent to that provided by most meals [*5*]. The intestine, therefore, must recover appropriate amounts of zinc from both dietary and endogenous sources to maintain a favorable zinc balance for the individual. Also of pancreatic origin is a low-molecular-weight molecule or zinc-binding ligand (ZBL) which presumably makes intraluminal zinc more available for absorption. The definitive chemical identity of this ZBL has not been established, although picolinic acid, citric acid, and various amino acids are candidates [*4*]. There is extensive evidence that the transfer of zinc from the intestinal mucosal cell to the body is homeostatically regulated by the zinc nutriture of the host [*6*]. Zinc is transported from the serosal surface of the intestine on albumin [*6*], and two-thirds of the portal zinc is taken up by the liver.

Peripheral, circulating zinc is firmly bound to α_2-macroglobulins (40 percent) and loosely bound to albumin and free amino acids (60 percent). The latter pool is involved in the nutritionally relevant transport and distribution. There does not appear to be any homeostatic mechanism, or zinc store, for maintaining circulating zinc levels constant. Consumption of a low-zinc, high-energy diet causes a lowering of serum zinc level and a subsequent increase in intestinal zinc absorption. Consumption of a low-zinc, low-energy diet promotes mobilization of amino acids from muscles to the liver for gluconeogenesis and also liberates zinc into the serum, maintaining circulating levels in the face of a developing depletion.

It is estimated that 60 percent of total-body zinc is in striated muscle, 20 percent in bone, 3.4 percent in liver, 2.1 percent in blood, 1.7 percent in the gastrointestinal tract, and 1.6 per-

cent in the skin [8]. The major route of excretion of zinc is via the feces, amounting to 1 to 2 mg/day of endogenous zinc, with an additional 500 μg/day in the urine. The remainder of excreted zinc is lost by integumentary routes such as hair, exfoliated skin, and apocrine secretions. A liter of sweat can contain over 1 mg of zinc; in hot, humid environments, sweat losses can contribute substantially to the output of zinc. Men lose around 1 mg in each ejaculum of seminal fluid, while lactating women lose from 0.5 to 4 mg of zinc per day in breast milk, depending on the stage of lactation.

BIOCHEMISTRY AND METABOLISM

The primary role of zinc is its function in metalloenzymes. Alkaline phosphatase, alcohol dehydrogenase, carboxypeptidase A, and superoxide dismutase are common mammalian zinc metalloenzymes. The role of zinc in protein synthesis and growth is probably also derived from its function in enzymes. The RNA polymerase and DNA polymerase of various microbial species are zinc metalloenzymes; it is likely that the respective mammalian enzymes also contain zinc. Two additional enzymes involved in nucleic acid metabolism—nucleoside phosphorylase and thymidine kinase—are also presumed to be zinc-dependent. In addition to its role in enzymes, *ionic* zinc is believed to contribute to the conformational integrity of polysomes and in stabilizing membranes, specifically of macrophages [9] and platelets [10].

INTERACTION WITH OTHER NUTRIENTS

Zinc interacts with a number of other nutrients. Vitamin A and zinc interact both in the transport of vitamin A from the liver on retinol-binding protein and in the conversion of retinol to its aldehyde form for the synthesis of the rhodopsin pigment (visual purple) for night vision [11]. The conversion of carotene to retinol is zinc-dependent, as is the absorption of conjugated folates from the intestine. High levels of dietary zinc reduce copper absorption in humans [12] and may increase ascorbic acid turnover [13]. Combined deficiencies of zinc and essential fatty acids had a synergistic effect on cutaneous manifestations in rodents, but were antagonistic in fowl [14]; the nature of the interaction of essential fatty acids and zinc deficiencies in humans has not been defined.

PATIENT

PATHOGENESIS OF ZINC DEFICIENCY

Zinc deficiency can develop by any one (or a combination) of various mechanisms, including: insufficient dietary intake, malabsorption, excessive excretion, or increased requirements. In addition to the dietary factors mentioned above, intestinal fistulas, short-bowel syndrome, mucosal disease, and pancreatic insufficiency can also reduce zinc absorption [4,15]. Pathological losses of blood or sweat can deplete the body of zinc, as can its excessive urinary excretion in renal disease, hypocaloric diets, and certain hormonal imbalances [15]. Rapidly proliferating malignancies will greatly increase demand for zinc. Pregnancy and lactation also increase zinc requirements beyond the basal demands.

CLINICAL MANIFESTATIONS

The clinical manifestations presently recognized to occur in zinc deficiency and to respond uniquely to therapeutic supplementation with zinc alone are listed in Table 122-2. Some, but not all, of these signs and symptoms can be related to the known functions of zinc metalloenzymes.

ASSESSMENT OF ZINC NUTRITURE AND DIAGNOSIS OF ZINC DEFICIENCY

Diagnosis

The evaluation of nutritional status with respect to zinc (Table 122-3) is limited by two factors: (1) the sophistication of the analytical instrumentation required; and (2) the lack of an unequivocal and representative index [16]. The most commonly employed index is zinc concentration in plasma or serum. This parameter is susceptible to invalidation by exogenous contamination, hemolysis, venous occlusion, steroid hormones, infections, hypocaloric diets, fasting, feeding, and abnormalities of plasma proteins. The zinc content of red cells, white cells, saliva, sweat, skin, nails, hair, and even cerumen—as well as the 24-h urinary zinc excretion and the urinary zinc-creatinine ratio—have also been used to assess zinc status.

Another approach has been to determine zinc-containing proteins (e.g., serum alkaline phosphatase, red cell carbonic anhydrase, white cell superoxide dismutase). Attempts to gauge *functional* indexes of zinc nutriture have included the determination of taste acuity, wound closure, sperm count, dark adaptation, phagocyte chemotaxis, and T-cell blastogenesis. The most definitive index of total-body zinc nutriture would be isotopic turnover studies and determinations of pool size.

Table 122-2. Clinical manifestations of zinc deficiency

Growth retardation	Immune deficiencies
Hypogonadism	Night blindness
Hypospermia	Impaired taste acuity
Alopecia	Delayed wound healing
Skin rashes	Behavioral disturbances
Diarrhea	

Table 122-3. Evaluation of zinc nutritional status

Measurement	Reported ranges of normal
Zinc content of:	
Serum*	140–65 μg/dL
Red cell	44–40 μg/g hgb
White cell*	130–80 μg per 10^{10} cells
Salivary (pure parotid)	79–23 ng/g
Sweat	1.75–0.55 mg/L
Skin	80–10 μg/g
Nail*	400–100 μg/g
Hair*	230–100 μg/g
24-h urine	600–230 μg/day

*Suggested for inclusion in the battery of measures for diagnosis, including taste acuity and/or dark adaptation.

Table 122-4. Ecological factors potentially reducing zinc nutriture in preindustrialized tropical countries

Geophysical factors:	Low zinc content of soil
Dietary factors:	High consumption of fiber, phytate
	Low consumption of meat, fermented whole-grain cereals or pulses, crustacea, and mollusks.
	High consumption of fishes, tubers, refined carbohydrates, fats, and oils
Cultural factors:	Geophagia
	Prolonged lactation and/or rapid succession of pregnancies
	Food taboos and food-processing methods
Climatic factors:	Hot, humid climate
Zoological factors:	Parasitoses
	Frequent episodes of infectious diarrhea

Newer advances in stable isotope technology portend safe, nonhazardous approaches to pool-size determination. Presently, when clinical zinc deficiency is suspected, a *battery* of parameters should be assessed, if possible. The diagnosis can only be made if several indexes converge and concur [*16*].

MANAGEMENT OF ZINC DEFICIENCY

Zinc deficiency arising in a clinical context can be managed by the administration of oral zinc supplements. Zinc sulfate, zinc gluconate, and zinc acetate are equally effective for this purpose. Daily zinc intake on the order of 150 mg for protracted periods (1 to 2 years) can induce copper deficiency [*17*]. It has been recommended that a dosage of 40 mg of zinc be the maximum limit for chronic administration [*18*]. Occasionally, zinc salts cause dyspepsia, nausea, and gastric irritation when ingested on an empty stomach. Mixing with food will reduce the symptoms but will also substantially reduce the biological availability of the supplemental zinc.

POPULATION

Ecological factors affecting zinc nutrition

A number of ecological factors may adversely influence zinc nutrition of populations (Table 122-4). Parasitic infection and diarrhea, so common in populations in developing nations, increase endogenous fecal zinc losses, while hot, humid climates increase sweat losses. Prolonged lactation and rapid succession of pregnancies increase maternal zinc needs. Food taboos often limit consumption of zinc-rich flesh foods during such periods, and also their use in the diet of sick people and/or rapidly growing children. Geophagy is common in people with hookworm, in pregnant women, and in young children in the tropics, but it is not clear if it is involved in provoking zinc deficiency or is a response to it. Food processing can increase availability of zinc, as in the traditional fermentation processes used in making wheat and soybean products. The fermentation hydrolyzes phytins. The refining of cereals and sugars, however, reduces the zinc content of such foods.

Most Brazilian Amazonian soils are poor in zinc as well as other essential minerals. It is probable that the zinc content of vegetation from such soils is also low, and that production of zinc-rich food sources from such soils is difficult without fertilizer. The fish, cassava, and refined carbohydrate diet of 1200 families in the Amazon Basin had a low zinc-to-energy density and only met 40 to 50 percent of the North American RDA for zinc [*19*]. Hair zinc levels of a population inhabiting an Amazonian tributary that drains zinc-poor soils were significantly lower than those from a population inhabiting a more fertile and zinc-rich central Amazonian flood plain [*19*].

Epidemiology of zinc deficiency

Zinc depletion has widely been reported as a feature of protein-energy malnutrition. If the established protein and zinc RDAs are correct, we must conclude that most foods and food mixtures are zinc-limiting before they are protein-limiting. For instance, the mean zinc-to-energy ratio of infant weaning food mixtures used as a breast milk supplement or substitute for 82 poor, urban infants in the Amazon was 47 percent of the RDA [*19*], lower than that shown to limit infant growth. In fact, addition of zinc to a recovery diet fed to Jamaican children with marasmus increased the rate of weight gain [*20*]. As evidence of a functionally important zinc depletion, supplementation of zinc to children with severe protein-energy malnutrition also has been shown to mobilize vitamin A from hepatic stores.

A syndrome of dwarfism and hypogonadism in children and adolescents in rural Egypt and Iran was attributed to zinc deficiency in the 1960s; the cause has been presumed to be in-

hibition of zinc absorption from the fiber- and phytate-rich diet of flatbreads, as this diet provided 11 to 12 mg of zinc.

Limited survey data are available regarding zinc nutriture in other developing nations. A large portion of pregnant Turkish women had low serum zinc concentrations, as did a quarter of all aborigines sampled in northwest Australia, whereas residents of the Tokelau Islands of Polynesia had normal values. In 382 poor, urban adults in the Amazon Valley, the mean zinc intake was found to be 49 percent of the RDA; serum zinc levels were below 70 μg/dL in at least a fourth of these individuals and showed a significant association with zinc intake [19]. In these same subjects, serum zinc was significantly correlated with zinc content of hair in the absence, but not in the presence, of gastrointestinal parasites. Natives of Papua, New Guinea, had lower hair zinc levels than urban Japanese and, in Central America, Panamanian children had low hair zinc content while Costa Rican children had normal levels. As discussed above, however, certainty of diagnostic classification is unfortunately not provided by any of these laboratory indexes.

Interaction of zinc nutriture and infection

Clinical observations in untreated patients with the congenital disorder of zinc malabsorption, *acrodermatitis enteropathica*, revealed a high incidence of intercurrent infections during life and thymic atrophy at necropsy, both suggestive of impaired immune defenses in zinc deficiency. Studies in laboratory animals have demonstrated thymic atrophy, reduced thymic hormone activity, diminished response of cultured lymphocytes to T-cell mitogens, decreased lymphokine production, and impaired antibody production to thymus-dependent antigens in experimental zinc deficiency [21]. Phagocytic function and neutrophil chemotaxis are also moderately impaired, while B-cell function is largely spared. Observations in human patients with zinc deficiency secondary to a number of pathological or iatrogenic conditions, including Down's syndrome and protein-energy malnutrition, confirm the widespread occurrence of zinc-responsive lesions in cellular immunity and phagocytic function [22].

The acute phase response to injury, inflammation, and stress involves the direct synthesis and secretion of a family of hepatic (acute-phase reactant) proteins. This is mediated by small polypeptides released by activated neutrophils and macrophages termed *leukocyte endogenous mediator(s)* (LEM). At least one highly purified molecule, endogenous pyrogen, has LEM activity, resulting in a precipitous decline in circulating zinc levels with its sequestration in the liver. The process involves de novo synthesis of hepatic metallothioneine and is also mediated by LEM. Later in the course of infection there is a transient hyperzincuria. Whether or not there are any consequences of this fall in plasma zinc for the nutrition of circulating cellular elements, including lymphocytes, granulocytes, or platelets, is not presently understood. This possibility is suggested by the finding of depressed zinc levels among patients with the lepromatous leprosy, characterized by suppressed cell-mediated immunity, but not with the tuberculoid forms [23]. The associated low iron and elevated copper levels—two other consequences of LEM activity—suggest that this trace mineral pattern in lepromatous leprosy is maintained by chronic endogenous mediator stimulation.

Prevention and control

Evidence that zinc deficiency constitutes a significant public health problem is convincing in only a few locations throughout the developing world at the moment. Continuing investigations may reveal additional foci of zinc malnutrition. It may be feasible to fortify some common food vehicle, such as sugar or salt, with an inorganic zinc compound, e.g., zinc carbonate, however, effectiveness studies of zinc fortification have not been reported under field conditions. Until a greater understanding of the diagnostic assessment is gained, and the performance of fortification programs is evaluated, systems for the control and prevention of zinc deficiency at the population level cannot be justified.

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