Zinc recently achieved the status of a micronutrient of established importance in human nutrition and medicine. Although a biological role for zinc was recognized more than 100 years ago, the first cases of human zinc deficiency were not described until the early 1960s. These initial reports were related to the syndrome of adolescent nutritional dwarfism found in children in Egypt and Iran. However, inadequate zinc in the diet was not appreciated as a nutritional problem in infants and children in the United States until the 1970s. Recent advances in technology—.concurrent with and partly responsible for progress in our understanding of the physiologic roles and nutritional importance of this metal—are beginning to permit application of new knowledge about zinc in clinical pediatrics.

Biochemistry and Physiologic Roles

The biologic importance of zinc stems primarily from its key role in many vital enzyme systems. More than 40 zinc-containing enzymes have now been identified, including at least one in every major enzyme classification. Examples include carbonic anhydrase, alkaline phosphatase, alcohol and glutamic dehydrogenases, and carboxypeptidases. Moreover, zinc appears to have a major role in nucleic acid metabolism and protein synthesis. Although the biochemical correlates of the features of zinc deficiency have not been elucidated completely, adverse effects on nucleic acid metabolism and protein synthesis may be responsible, in part, for the impaired growth and development that are prominent signs of the zinc-deficient state both before and after birth. Maternal zinc deficiency in the rat results in intrauterine growth retardation and a high incidence and wide spectrum of congenital malformations in the offspring. Perinatal zinc deficiency in the rat can cause impairment of brain growth and of subsequent learning ability and behavioral development. Postnatally, the most prominent features of zinc deficiency in the young animal are anorexia and growth retardation, and utilization of absorbed food is impaired.

In later stages of development, zinc deficiency causes hypogonadism and delayed sexual maturation. Pituitary function appears to remain intact, but testosterone synthesis in the testes is impaired. Zinc is necessary for normal keratogenesis, and zinc-deficient animals may manifest alopecia, a variety of skin lesions, and impaired wound healing. Skeletal lesions, diarrhea, and an increased susceptibility to infection are other documented symptoms of zinc deficiency. Zinc may participate in the synthesis, storage, and/or release of insulin from the beta cells. However, the effects of zinc deficiency on plasma insulin levels and glucose tolerance have been inconsistent. Mobilization of vitamin A from the liver is decreased in zinc-deficient rats, and serum vitamin A levels are depressed. Zinc is necessary for normal growth at a cellular level, which may explain why the nutritional requirements for this metal are particularly high in the young of all species investigated. Requirements for the young male animal may be higher than those for the female.

Zinc Metabolism and Body Distribution

Zinc is absorbed via the small intestine. A low molecular weight ligand secreted by the pancreas appears to have a physiologic role in the absorption process, but the mechanisms are not completely understood. The adult human body contains approximately 2 gm of zinc, which is about half the body content of iron and 20 times that of copper. Highest concentrations of zinc occur in the choroid of the eye and in the spermatozoa. Concentrations exceeding 100 μg/gm are present in hair, nails, the prostate gland, and bone; and liver, kidney, muscle, and skin have about 50 μg/gm wet weight. Lower concentrations are present in other tissues; for example, erythrocytes contain 12 to 14 μg of zinc per gram, and most of this zinc is incorporated into carbonic anhydrase. The zinc in plasma (approximately 90 μg/dl) is bound to albumin, and α2-macroglobulin, and transferrin. The albumin-bound zinc is in equilibrium with a small amino acid-bound frac-
tion, and the latter is thought to be the major source of the zinc excreted in the urine.\textsuperscript{18} Approximately 0.5 mg of zinc is excreted each day in the urine of adults, and a similar quantity is excreted in the sweat. The primary route of excretion of endogenous zinc is via the feces, which also contains substantial quantities of dietary zinc that were not absorbed.

**Dietary Sources and Nutritional Requirements**

Approximate nutritional requirements for zinc can now be given. The first recommended dietary allowances for zinc for children were published in 1974\textsuperscript{19} by the Food and Nutrition Board of the National Academy of Sciences. The recommendations for infants and children are 3 mg/day from birth to 6 months, 5 mg/day from 6 to 12 months, 10 mg/day from 1 to 10 years, and 15 mg/day for older children and adolescents. The requirements depend to some extent on the weight and age of the infant or child and on the rate of growth. Moreover, the bioavailability of this metal varies considerably according to the dietary source. The quantity of zinc absorbed may range from 20% to 60% of that ingested. In general, meats and fish are the best known sources of zinc, and the zinc from animal protein is better absorbed than that from vegetable sources. Phytate and fiber in the diet decrease the availability of the zinc for absorption,\textsuperscript{20} and the use of soy protein as meat and milk substitutes may adversely affect zinc nutriture. Substantial quantities of zinc can be lost during food processing, such as the milling of wheat and the refining of sugars.\textsuperscript{21} White bread, refined sugars, vegetables other than legumes, and fruits contain relatively little zinc. Published information on the zinc content of foods\textsuperscript{22-24} is now adequate enough to permit a reasonable estimate of total dietary zinc intake, which can vary considerably depending on the individual’s diet.

The zinc concentration in human colostrum reaches as high as 20 mg/liter,\textsuperscript{25} and in breast milk it averages 3 mg/liter for the first one to two months of lactation. The zinc concentration declines further as lactation progresses. In cow’s milk the zinc concentration ranges from 2 to 7 mg/liter, with a mean of about 3.5 mg/liter. There is some evidence that the bioavailability of the zinc for the human infant is less from cow’s milk than from human milk. Cow’s milk formulas are now generally supplemented with zinc to a level of 3 to 4 mg/liter, and larger supplements have been added to soy-based formulas. However, clarification of the optimal quantity of zinc supplement depends on a better understanding of the relative bioavailability of zinc from different milk sources.

**Zinc Deficiency Encountered in Pediatric Practice**

Zinc deficiency in infants and children can result from inadequate dietary intake, impaired absorption, excessive excretion, and an inherited defect in zinc metabolism. Impaired growth has been documented in otherwise healthy male infants fed a milk formula containing less than 2 mg of zinc per liter\textsuperscript{26}; these formulas were in widespread use until 1975, when it became a general practice to supplement them with zinc to a level equivalent to that of cow’s milk. Less information is available on the zinc nutriture of children, but some otherwise healthy school-aged children may have a suboptimal zinc intake, with adverse effects on appetite, taste perception, and growth.\textsuperscript{6} A high incidence of low biochemical indices of zinc nutriture has been reported among preschool-aged children from low-income families.\textsuperscript{27} More severe zinc depletion has occurred in children\textsuperscript{28} and adults\textsuperscript{29} receiving total parenteral nutrition without zinc supplements. Some of these children have developed a syndrome similar to acrodermatitis enteropathica, including anal and orificial skin lesions, diarrhea, alopecia, and depression.

The pathogenesis of the rare, inherited disease, acrodermatitis enteropathica, is now known to be attributable to a serve zinc deficiency,\textsuperscript{30-32} which is probably secondary to an inherited defect in zinc absorption.\textsuperscript{33} This is the most severe human zinc deficiency syndrome yet identified; and, if it is untreated in early childhood, death results. A rapid, complete, and sustained clinical remission is uniformly achieved with oral zinc therapy in a sufficient dose to overcome the deficiency. An increased susceptibility to infection is characteristic of acrodermatitis enteropathia, and it may be related in part to zinc-responsive defects in leukocyte function.\textsuperscript{34} Women with this disease who have survived without zinc therapy have infants with a high incidence of congenital malformations similar to those observed in zinc-deficient rats.\textsuperscript{35}

Acquired zinc deficiency can occur as a result of impaired absorption of this metal. The large quantities of phytate\textsuperscript{36} and fiber\textsuperscript{27} in the diet of the rural population in Iran are thought to be major etiologic factors in the zinc deficiency of adolescents with nutritional dwarfism in that country.\textsuperscript{1-5} Although information remains sketchy, conditioned zinc deficiency appears to
be a potential complication of intestinal malabsorption syndromes. If steatorrhea is present, zinc may form insoluble complexes with fat and phosphates. Therefore, the possibility of this complication should be considered in diseases such as cystic fibrosis, regional enteritis, and celiac disease. Excessive zinc excretion resulting from chronic blood loss, excessive sweating, or hyperzincuria may also lead to a significant depletion of this metal. Hyperzincuria has been proposed as a mechanism for zinc depletion in persons with sickle cell disease. Excessive urinary loss of zinc occurs in a variety of other conditions, including catabolic states, liver diseases such as acute infectious hepatitis, burns, diabetes mellitus, and the nephrotic syndrome. Iatrogenic hyperzincuria occurs in association with the use of chelating agents, diuretics, corticosteroids, and intravenous administration of protein hydrolysates and amino acid infusates.

The earliest and frequently the only sign of zinc deficiency in infants and young children is a decline in growth velocity, which may be accompanied by an obvious impairment of appetite. Pica may occur, and abnormalities of taste perception may be demonstrable. When nutritional zinc deficiency is severe, growth suppression is severe, sexual maturation is arrested, and symptoms may include any or all of those that occur with acrodermatitis enteropathica.

Detection and Diagnosis

The possibility of zinc deficiency should be considered if there are suggestive clinical symptoms or predisposing circumstances. Confirmation can be provided by a low plasma zinc level. However, despite the relative simplicity of this assay, a number of limitations and potential pitfalls have to be considered:

1. The risk of sample contamination during collection or processing is substantial. Containers with rubber caps should not be used.

2. The mean value for normal subjects is approximately 90 μg/dl of plasma, with a lower limit of normal of 65 to 70 μg/dl. However, significant variations still exist between different laboratories. Normal serum values are thought to be slightly higher than those of plasma.

3. Plasma zinc levels can be depressed, even without body depletion of this metal, during any acute or chronic infection or in a number of other circumstances.

Currently, it is not known if the normal range of plasma zinc levels for infants is lower than that for children and adults.

Determination of the zinc concentration in hair may also be useful, but this test should not be regarded as a substitute for determining the plasma zinc levels because there is no correlation between zinc levels in plasma and hair. However, a low hair zinc level appears to be useful in the detection of chronic, mild zinc deficiency in children in whom the plasma zinc level may not necessarily be depressed at the time of a solitary blood collection. Hair zinc concentrations less than 70 μg/gm may provisionally be considered abnormal; this may apply to levels up to 100 μg/gm. However, it is not certain that these levels also apply to infants and toddlers. The hair analyses should be restricted to a short section of hair taken from close to the scalp. Hair zinc concentrations are affected by variations in the rate of hair growth. Measurement of zinc concentrations in other tissues and fluids (e.g., saliva) is less well established. Twenty-four-hour urine excretion rates can be useful in the confirmation of moderate or severe deficiency states, in the detection of hyperzincuria, and in monitoring the results of therapy (e.g., in acrodermatitis enteropathica). Serum alkaline phosphatase levels may be depressed, and an increase in activity after zinc supplementation is commenced provides useful confirmation of the diagnosis of zinc deficiency.

Detection of marginal nutritional zinc deficiency is particularly difficult. Except for laboratory measurements, or in lieu of these if they are unavailable, calculation of the dietary zinc intake is helpful. If the intake is or has been low and there are nonspecific symptoms such as declining growth percentiles and feeding problems, a trial of dietary zinc supplementation is justified.

Treatment

The quantity of zinc required for the treatment of zinc deficiency depends on the circumstances. For a simple nutritional deficiency, supplementation with 0.5 to 1 mg of zinc per kilogram of body weight per day, a quantity similar to the upper limits of the range of normal dietary intake, is probably both adequate and safe. Somewhat larger quantities may be needed if there is impaired intestinal absorption or an excessive loss of zinc. All patients with acrodermatitis enteropathica should now be treated with 10 to 45 mg of zinc per day. Therapy should be monitored in an adequately equipped center to determine the optimal quantities of zinc for the individual patient. Patient on long-term intravenous feeding should have plasma zinc determinations at regular intervals. If the plasma zinc levels decline (or cannot be determined), sufficient quantity of zinc...
should be added to the infusate to provide 30 to 50 μg of zinc per kilogram of body weight per day. Larger quantities may be required if there are excessive losses, for example via jejunostomy fluids.

Zinc has been used pharmacologically in the management of surgical patients, in patients with sickle cell disease, and in patients with rheumatoid arthritis. However, zinc should not be used to treat infants and children without evidence of zinc deficiency, and the dose should be sufficient only to treat the deficiency. Although zinc therapy is sometimes prescribed for children with learning disorders, there is no scientific basis for this practice.

Zinc has been administered most frequently as the sulfate; however, zinc sulfate can be a gastrointestinal irritant in some individuals, even at a relatively low dose. Thus, an alternative, soluble zinc salt, such as the acetate, should be used. An example of a convenient solution for infants and young children is 13 mg of zinc acetate (approximately 1 mg of zinc) per milliliter. This dosage form can be administered in two or three divided doses per day, preferably at least one hour before meals.

Zinc is relatively low in toxicity, and, in physiologic quantities, it appears to be entirely safe. If larger quantities are given (e.g., for acrodermatitis enteropathica or when supplementation is prolonged), levels should be monitored, at least in plasma, to ensure that they do not exceed the physiologic range. Although increasing the zinc/copper ratio of rat diets has been reported as a cause of hypercholesterolemia, this condition appears to be related to an absolute deficiency of copper. Nevertheless, a gross excess of zinc can interfere with copper absorption and metabolism.

Conclusions

Zinc deficiency can occur in infants and children as a result of inadequate dietary zinc intake, disturbed zinc metabolism secondary to numerous disease states, and an inherited defect in zinc metabolism in acrodermatitis enteropathica. In the latter condition, the effects of zinc therapy are dramatic and potentially lifesaving. Symptoms can also be severe in conditioned zinc deficiency states, and it is clinically important to recognize the need for zinc therapy in this condition. Clinically less severe, but probably much more widespread, is marginal nutritional zinc deficiency. Although the extent of this condition is unknown, some preventative measures have recently been undertaken, including zinc supplementation of "low-zinc" infant formulas and zinc fortification of some ready-to-eat breakfast cereals. But the effectiveness of these measures will have to be assessed.

The possibility of zinc deficiency should be considered in infants and children whose growth percentile declines, even those who seem otherwise healthy.

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