

Zinc and Copper: Evidence for Interdependence, Not Antagonism

In this issue of *Nutrition*, a twist on zinc–copper antagonism is brought to the forefront in a very compelling study in humans.¹ High levels of zinc in the diet impede the bioavailability of copper at the absorption stage.² Studies with animals have shown repeatedly that high zinc intakes tend to suppress inward movement of copper through the gut and into select tissues.^{3–6} Studies have investigated whether these same interactions apply to or occur in humans.^{7,8} The animal studies have tended to focus on the induction of metallothionein by zinc and subsequent sequestering of copper secondarily by the heavy metal binding protein. Although designed primarily to protect the organ or animal from heavy-metal toxicity, metallothionein elevation can deprive a system of adequate amounts of copper and, hence, provide the foundation for developing copper deficiency. The evidence by Milne et al.¹ at the Grand Forks Human Nutrition Research Center shows clearly that in humans the two metals antagonize one another only at high levels but that zinc at adequate levels might be beneficial, if not required for copper use.

The idea that zinc interferes with copper metabolism can be traced as far back as 1946, when Smith and Larsen reported that excess copper overcame zinc-induced anemia in rats.⁹ The copper alleviated the symptoms of zinc toxicity, presumably by blocking zinc accumulation in the liver. Although experiments since have tended to use zinc or copper as the protagonist, the imprint of one metal on the other in a competitive fashion or through metallothionein elevation has been entrenched in the minds of nutritionists for decades. For example, because of its ability to block copper absorption, zinc at high levels has become an accepted therapy for alleviating the copper buildup in Wilson's disease in humans.¹⁰ Thus, a study that purports to show that zinc is necessary for the proper metabolism of copper is swimming upstream against some well-established nutritional phenomena.

What makes the Grand Forks study unique, however, is the use of human subjects confined to an isolation facility and fed rigorously controlled diets that closely emulate standard intakes of copper and zinc. Precision of analysis and assurance of compliance are beyond reproach. The 21 postmenopausal women who took part in the study were fed isocaloric diets (2000 kcal) containing 1 or 3 mg of copper and 3 or 53 mg of zinc over 90 d, with 10-d adjustments between regimens. Copper balance was determined for each treatment. In addition, the typical parameters of copper adequacy or deprivation, namely serum copper, serum ceruloplasmin, serum cholesterol, and glutathione, and platelet levels of cytochrome-C oxidase were monitored routinely, as were erythrocyte glutathione peroxidase and superoxide dismutase.

The result of the study provides clear evidence that low levels of zinc are more detrimental than high levels to copper use. For example, immunoreactive ceruloplasmin and platelet cytochrome-C oxidase activities were significantly lower during periods of low dietary zinc. Likewise, blood glutathione and erythrocyte glutathione peroxidase were lower when zinc was low. Overall, most indices of copper status seemed to be negative when copper was adequate but zinc was inadequate. This finding means that an

individual requiring copper for physiologic function has a greater risk of inadequacy from low than from high levels of zinc. Although these data may seem non-conformist to the tradition of zinc versus copper, they are forceful reminders that nutrition is more than a question of oral intake. How the systems use the zinc and copper as these elements course through tissues and enzymes requires an equal amount of attention. Where zinc and copper cross paths for the mutual benefit of either metal should become an important concern in human nutrition.

Edward D. Harris, PhD
*Department of Biochemistry
 and Faculty of Nutrition
 Texas A&M University
 College Station, Texas, USA*

REFERENCES

1. Milne DB, Davis CD, Nielsen FH. Low dietary zinc alters indices of copper function and status in postmenopausal women. *Nutrition* 2001;17:701
2. DiSilvestro RA, Cousins RJ. Physiological ligands for copper and zinc. *Annu Rev Nutr* 1983;3:261
3. Murthy L, Klevay L, Petering HG. Interrelationships of zinc and copper nutrition in the rat. *J Nutr* 1974;104:1458
4. L'Abbé MR, Fischer PWF. The effects of dietary zinc on the activity of copper-requiring metalloenzymes in the rat. *J Nutr* 1984;114:823
5. Fischer PWF, L'Abbé MR. Copper transport by intestinal brush border membrane vesicles from rats fed high zinc or copper deficient diets. *Nutr Res* 1985;5:759
6. Oestreicher P, Cousins RJ. Copper and zinc absorption in the rat: mechanism of mutual antagonism. *J Nutr* 1985;115:159–166
7. Prasad AS, Brewer GJ, Schoemaker EB, Rabbani P. Hypocupremia induced by zinc therapy in adults. *JAMA* 1978;240:2166
8. Kelsay JL, Jacob RA, Prather S. Effect of fiber from fruits and vegetables on metabolic responses of human subjects. III. Zinc, copper and phosphorous balances. *Am J Clin Nutr* 1979;32:2307
9. Smith SE, Larson EJ. Zinc toxicity in rats. Antagonistic effects of copper and liver. *J Biol Chem* 1946;163:29
10. Brewer GJ, Yuzbasiyan-Gurkan V, Lee D-Y, Appelman H. Treatment of Wilson's disease with zinc. VI. Initial treatment studies. *J Lab Clin Med* 1989; 114:633

PII S0899-9007(01)00615-3

Breast Feeding, Infant Formulae, and Oral Tolerance

The review by Exl and Fritsché¹ in the July/August issue of *Nutrition* raises a number of questions concerning the induction of oral tolerance in early life. These issues are not only practically important in the prevention of food allergy but may provide insight into the mechanisms of oral tolerance.

Early postnatal life is thought to be a vulnerable time for the development of adverse food reactions. The current view is that the establishment of food tolerance depends on the presentation of food antigens to naive T cells without costimulation.² More correctly, at low levels of expression, costimulatory molecules on

Correspondence to: Edward D. Harris, PhD, Department of Biochemistry and Biophysics, 2128 TAMU, Texas A&M University, College Station, TX 77843-2128, USA. E-mail: eharris@tamu.edu

Correspondence to: Colin H. Little, MBBS, MRCP(UK), FRACP, 324 Stephenson's Road, Mt. Waverley, Melbourne, Victoria 3149, Australia. E-mail: littlec@bluep.com