What Types of Nutrition Research Give the Best Benefits?

In this high-tech era of molecular biology, designer-drug therapies and gene therapy, good nutrition absolutely remains the single most cost-effective way to improve the health and well-being of the greatest number of individuals on our planet. For most people, learning what a "healthy diet" is and how to provide a seasonably variable diet that provides the basic nutrients needed for health is the greatest single nutritional challenge for creating improved health in the Western and developing countries alike.

In the Western countries we cumulatively spend hundreds of millions of dollars studying how to use molecular biology, designer-drug therapies, and gene therapy to prevent and treat our Western diseases, such as heart disease, diabetes, cancer, and obesity. Although understanding the biochemical pathways that are responsible for these diseases is important, there remain substantial problems with regard to cost effectiveness. Given that these Western diseases have been absolutely linked to what we also call the Western diet, perhaps we need to consider our approach to disease prevention and treatment. Even in the most affluent Western countries, the disease therapies that use these expensive new technologies will remain financially unattainable for many persons with access to the best state-run or privately run health care systems and will remain so for decades to come, if not forever. But when one looks at poor countries, such as Nepal, where the yearly per capita income hovers near $1100, the "solutions" promised by high-tech medicine will remain forever inaccessible. This indeed is the reality for most people on the planet.

The immense funds we divert toward what Dr. Temple calls "complex research" prevent our understanding of what basic preventative nutrition should be in Western and developing countries alike. In contrast, "simple research" consists of epidemiologic and intervention trials that seek to directly identify the factors that cause or prevent disease. This is augmented by the use of biochemical and physiologic measurements primarily as indicators of disease risk. Dr. Temple nicely highlights some of the problems inherent in what he calls "complex research." This is research where in vitro biochemical and cell culture observations are used as the primary method for generating hypotheses to be tested by larger, more expensive, and complicated clinical trials.

Recent studies on vitamin E and β-carotene[1,2] are classic reminders of how ideas that start as in vitro biochemical observations often fail to generate conclusions that can be supported by labor-intensive and enormously expensive intervention studies. Even though we will undoubtedly continue to discover how the genetic heritage of individuals and populations place us at risk for specific forms of malnutrition, it is a reality that the era of discovering diseases caused by single nutritional factors are pretty much gone. This may be a difficult reality for many nutrition researchers to accept and is the cause for a need to change our perspective.

It is more probable that minerals, vitamins, and other nutrients in our foods act synergistically to prevent disease and promote health. There is very little chance that the entire world's population could benefit from any single nutritionally derived molecule that can be identified from complex research, biochemically isolated and placed in a pill, inserted into a grain of rice, or transfected into the human genome cost effectively to reduce our risk for Western diseases.

The Western diseases are for the most part caused by a multitude of nutritionally related factors linked to the Western diet, with additional confounding from genetics, lifestyle clusters, exercise, and exposure to environmental carcinogens. There are no easy solutions on to how to deal with the problem of confounding in studies of nutrition and these diseases. However, Dr. Temple makes light of some of the approaches to recognizing the problems with confounding and limiting its influence on study results. The first and foremost method to limit confounding problems is, of course, the inclusion of large numbers of participants. Although expensive, when these large studies use biochemical and physiologic measurements as indicators of disease risk, these cohort studies clearly have had the most impact on improving our lifestyle through improved nutrition.

Wide disparities will always be present with regard to access to medical technology, yet healthy food will always remain the most available method for people of the Western and developing countries to remain healthy. It is for these reasons that simple research using large cohort studies will remain the single most cost-effective way to most equitably improve the health of the largest number of people on our already crowded planet.

Ted Wilson, PhD
Department of Exercise and Sport Science
University of Wisconsin–La Crosse
La Crosse, Wisconsin, USA

REFERENCES

1. Temple NJ. Nutrition and disease. Nutrition 2002;18:343
2. Alpha-Tocopherol, Beta Carotene Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029
3. Rapola JM, Virtamo J, Ripatti S, et al. Randomised trial of alpha-tocopherol and beta carotene supplements on incidence of major coronary events in men with previous myocardial infarction. Lancet 1997;349:1715

PII S0899-9007(01)00791-2

Intestinal Zinc, Iron, and Copper During the Perinatal Period

Although a substantial body of research on human-milk composition and the advantages of breast feeding have increased our knowledge on the subject, there are some unanswered questions pertaining to the pattern of trace-element concentrations in human milk and nutritional consequences for breast-fed infants. The well-regulated mechanisms that transfer zinc, iron, and copper from maternal plasma to the mammary gland allow only a certain amount of these elements to pass to milk through specific carrier proteins. Whereas this regulatory process maintains iron and copper at relatively constant levels throughout lactation, high zinc concentration, characteristic of colostrum, decreases during the period of the infant's high nutritional demand, thus raising important considerations. Data from comprehensive reviews of zinc[1] and iron and copper[2] in breast milk are shown in Figure 1.

A positive nutrient balance and a nutrient intake proportional to somatic growth are expected during the infant's fast growth period coupled with increased metabolic functions due to organ maturation. Although this is the case for most nutrients provided in breast milk, the infant's hepatic reserves compensate for the low concentrations of trace elements in breast milk, especially iron and copper. However, in early postpartum days, there is a decrease in the infant's total zinc intake due to a sharp fall in milk zinc concentration not compensated for by the increased milk yield. In

---

Correspondence to: Ted Wilson, PhD, Department of Exercise and Sport Science, University of Wisconsin—La Crosse, La Crosse, WI 54601, USA. E-mail: wilson.edwa@uwlax.edu

Correspondence to: José G. Dórea, PhD, CP 04322, Universidade de Brasilia, 70910-979 Brasilia DF, Brazil. E-mail: dorea@rudah.com.br

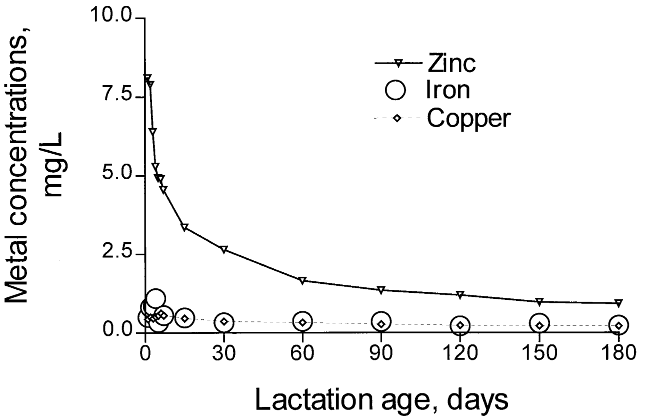

FIG. 1. Median concentrations of zinc,[1] iron, and copper[2] in human milk as function of lactation age.

addition, during the perinatal period there is a negative zinc balance in term infants that lasts longer in preterm infants.[3] This "excessive loss" of lumenal zinc in the infant's feces seems to be the result of an increase in the exchangeable zinc pool[4] but also may represent a pathophysiologic asset associated with gastrointestinal maturation during the transition from intra- to extrauterine life.

The important changes related to organ growth, morphologic differentiation and functional maturation of the intestines, are associated with colostrum ingestion.[5] Colostrum is high in zinc but relatively low in iron and copper (Fig. 1), thus creating high ratios of zinc to those elements. Such ratios can range from 8.26 to 15.4 for zinc to iron and from 7.14 to 41 for zinc to copper.[1,2] It may not be a coincidence that the chemical composition of meconium shows that zinc is higher than either copper or iron, with a zinc-to-iron ratio of 3 to 7 and a zinc-to-copper ratio of 3.5 to 4.[1,2]

The concentrations of metals leaving (with meconium) or entering (with colostrum) the intestinal milieu reflect metabolic events or infant needs peculiar to the transition from fetal (intrauterine) to neonatal (extrauterine) life. However, the importance of such a micronutrient balance has not been fully comprehended. The physiologic "excess" of zinc in relation to iron and copper in colostrum and meconium may benefit the immature organism in the prenatal and neonatal stages. If so, proprietary formulas or breast-milk substitutes do not maintain the proportions of zinc to iron and zinc to copper found in human milk.

Besides specific immunoproteins, the protective effect conferred by human milk may be through its peculiar chemical composition. One such characteristic, the iron-withholding bacteriostatic activity, is an important defense against pathogenic microorganisms. A low concentration of tightly bound iron, coupled with a high zinc-to-iron molar ratio, can enhance such a bacteriostatic effect. In vitro studies have demonstrated that zinc enhances the iron-binding capacity of lactoferrin.[6] Marchetti et al.[7] showed that zinc-saturated lactoferrin as opposed to other milk proteins, such as α- and β-lactoglobulin, was the sole compound capable of inhibiting a phase of infection of polivirus type 1 internalization into host cells. Further, saturation of milk lactoferrin with iron leads to loss of its bacteriostatic property.[8]

During a short postpartum period, there is an emergence of antioxidant enzymes that are fundamental in protecting newborns against free radicals.[9] Also, protection against oxidant injury can be accomplished by the antioxidant effect of iron depletion.[10] Therefore, it is worth noting the warning of Weinberg[11] with regard to the potentially hazardous amounts of iron in infant formulas.

Although the ratio of zinc to copper in plasma can be a predictor of mortality in patients infected with human immunodeficiency virus type 1,[12] it is unclear whether an excess of zinc in relation to copper could also benefit the immature organism in the prenatal or neonatal stages. Excess dietary zinc slows down intestinal copper absorption. After supplementing breast milk with zinc and copper to increase their concentrations to 8 and 0.4 mg/L, respectively (zinc:copper, 20), Ehrenkrantz et al.[13] found a significantly higher excretion of copper in premature infants. Such metal concentrations are comparable to the upper limits of colostrum concentrations. Besides the decreased absorption of iron or copper and a substantial decrease in percentage of net absorption and retention of copper, no other adverse effect was observed in formula testing studies.

Present concepts of formula or breast feeding have not sufficiently addressed trace-mineral imbalances or suboptimal zinc nutrition status during the perinatal period. Nevertheless, the concerns about iron supplementation seem central in pediatric nutrition. Meanwhile, evidence shows that, at early ages even with breast feeding, zinc deficiency or suboptimal zinc nutrition status is an important issue in pediatric nutrition.[1] A metabolic role designed to protect the transitional immaturity of the young infant from harmful pathogens or chemical insults could benefit from the peculiar pattern of zinc in relation to copper and iron in human milk.

José G. Dórea, PhD
Department of Nutrition
Universidade de Brasilia
Brasilia, DF, Brazil

REFERENCES

1. Dorea JG. Zinc in human milk. Nutr Res 2000;20:1645
2. Dorea JG. Iron and copper in breast milk. Nutrition 2000:16:209
3. Higashi A, Ikeda T, Iribe K, Matsuda I. Zinc balance in premature infants given the minimal dietary zinc requirement. J Pediatr 1988;112:262
4. Hambidge KM, Miller LV, Krebs NF, et al. Estimation of the total size of pools of zinc that exchange with plasma within two days in normal infants and adults. In: Anke M, Meissner D, Mills CF, eds. *Trace elements in man and animals.* TEMA-8, 1993:1105
5. Xu RJ. Development of the newborn GI tract and its relation to colostrum/milk intake: a review. Reprod Fertil 1996;8:35
6. Ainscough EW, Brodie AM, Plowman JE. Zinc transport by lactoferrin in human milk. Am J Clin Nutr 1980;33:1314
7. Marchetti M, Superti F, Ammendolia MG, et al. Inhibition of polio virus type 1 infection by low, manganese- and zinc saturated lactoferrin. Med Microbiol Immunol 1999;187:199
8. Bullen JJ, Rogers HJ, Griffiths E. Nutrient deficiencies in breastfed infants. N Engl J Med 1978;299:1471
9. Saugstad OD. Oxygen toxicity in the neonatal period. Acta Paediatr Scand 1990;79:881
10. Sullivan JL. Antioxidant effects of iron depletion. Free Radic Biol Med 1994; 17:87
11. Weinberg ED. Role of iron in sudden infant death syndrome. J Trop Exp Med 1994;7:47
12. Lai H, Lai S, Shor-Posner G, et al. Plasma zinc, copper, copper: zinc ratio, and survival in a cohort of HIV-1-infected homosexual men. J Acquir Immune Defic Syndr 2001;27:56
13. Ehrenkranz RA, Gettner PA, Nelli CM. Nutrient balance studies in premature infants fed premature formula or fortified preterm human milk. J Pediatr Gastroenterol Nutr 1989;8:58

PII S0899-9007(01)00737-7