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Special Issue on Recent Intervention Trials with Zinc: Implications for Programs and Research

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The importance of zinc in human nutrition and estimation of the global prevalence of zinc deficiency

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Abstract

This paper summarizes recent research on the importance of zinc for human health, and reviews available methods of evaluating zinc status in individuals and populations. The lack of generally accepted biomarkers of zinc status has impeded estimation of the global prevalence of zinc deficiency. Although measurement of zinc consumption and/or plasma zinc concentration can be used to assess population zinc status, few countries have collected adequate data to permit estimation of the prevalence of zinc deficiency. An alternative method, described herein, is to estimate the zinc content of national food supplies, using FAO food balance sheets; the assumed bioavailability of that zinc based on phytate:zinc molar ratios; and the relation between absorbable zinc and theoretical requirements according to country-specific demographics. The results of these analyses indicate that nearly half of the world's population is at risk for inadequate zinc intake, suggesting that public health programs are urgently needed to control zinc deficiency.

Zinc in the environment and in biology

Zinc is a bluish-white metallic element (atomic number 30, atomic weight 65.4), which makes up about 0.02% of the earth's crust and is the twenty-third most abundant element. Because of its nature as a transitional element in the periodic table, zinc possesses certain chemical properties that make it especially useful and important in biological systems. Specifically, zinc is able to constitute strong, but readily exchangeable and flexible, complexes with organic molecules, thereby enabling it to modify the three-dimensional structure of nucleic acids, specific proteins, and cellular membranes and influence the catalytic properties of many enzyme systems and intracellular signaling. Zinc is associated with more than 50 distinct metalloenzymes, which have a diverse range of functions, including the synthesis of nucleic acids and specific proteins, such as hormones and their receptors [1]. For these reasons, zinc plays a central role in cellular growth, differentiation, and metabolism. Of further interest is zinc's absence of redox properties, which allows it to be transported in biological systems without inducing oxidant damage, as can occur with other trace elements such as iron and copper.

Prasad [2] reviewed the early history of research on the biological importance of zinc. To summarize from his report, zinc was first recognized as an essential nutrient for microorganisms more than 125 years ago. Appreciation of its essentiality for higher plants, rats and mice, poultry, and swine followed during the period from the 1920s through the 1950s. Despite these observations, researchers remained skeptical about the possibility of zinc deficiency in humans because of the element's ubiquity in the environment. Nevertheless, evidence of human zinc deficiency began to emerge in the 1960s, when cases of zinc-responsive dwarfism and delayed sexual maturation were first reported among Egyptian adolescents. Since then, clinical studies of children with acrodermatitis enteropathica, an inborn error of zinc metabolism resulting in poor zinc absorption and consequent severe zinc deficiency, have confirmed the critical role of zinc in physical growth and gastrointestinal and immune function [3]. Moreover, as described below, zinc intervention trials have produced positive growth responses and reduced rates of infections in high-risk children of vulnerable populations.

Zinc metabolism

Zinc is absorbed into the body through the small intestine, which also regulates whole-body homeostasis

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through changes in both the fractional absorption of dietary zinc and excretion of endogenous zinc in pancreatic juice and other gastrointestinal secretions [4, 5]. Some zinc is also lost from the body through urine, menstrual flow, semen, and sloughed skin, nails, and hair, although quantitatively these other routes of zinc loss are relatively small compared with gastrointestinal excretion [5]. As with intestinal excretion, the urinary elimination of zinc can be affected by zinc status [6], although this effect is less consistent and may only occur with more severe or prolonged dietary restriction. Fecal zinc excretion is also increased during diarrhea [7], which may contribute to zinc deficiency in areas with high rates of enteric infections.

The total body zinc content of adult humans ranges from about 1.5 to 2.5 g, most of which is found intracellularly, primarily in muscle, bone, liver, and other organs [4]. Approximately 90% of the body's zinc reserves turn over slowly and are therefore not readily available for metabolism. The remaining zinc comprises the so-called rapidly exchangeable pool of zinc, which is thought to be particularly important for maintaining zinc-dependent functions of human biological systems. The rapidly exchangeable zinc can move into and out of the plasma compartment within a period of about three days. The size of this pool is sensitive to the amounts of zinc absorbed from the diet, and a reasonably constant dietary supply is thought to be necessary to satisfy the normal requirements of zinc for maintenance and growth.

Less than 0.2% of the total body zinc content circulates in plasma, which has a mean concentration of approximately 15 µmol/L (about 100 µg/dl). Zinc is transported in plasma bound to albumin and, to a lesser extent, α_2-macroglobulin and oligopeptides [1]. Because the concentration of zinc in tissues, such as muscle and liver, is approximately 50 times greater than that in plasma, small differences in uptake or release of zinc from these peripheral sites can have a profound effect on the plasma zinc concentration. For these reasons, plasma zinc concentrations do not indicate total body zinc stores reliably under all circumstances in individual subjects. For example, release of zinc from muscle tissue that is catabolized during starvation can result in transient, seemingly paradoxical, elevations in plasma zinc [8]. In contrast, consumption of standard meals, or glucose alone, induces a postprandial reduction in plasma zinc concentration, even though dietary zinc intake and tissue reserves may be adequate [9]. Other factors that influence plasma zinc concentration are hypoalbuminemia, which influences absorption and transport of zinc [10]; intestinal diseases that interfere with zinc absorption [11]; pregnancy [12]; infection [13–15]; and other forms of stress, such as tissue injury imposed by surgery [16] and strenuous physical exercise [17].

Zinc and human function

Since the early reports of human zinc deficiency, and particularly during the past 10 to 15 years, a considerable number of well-designed clinical trials have been completed to examine the relationships between zinc supplementation and human health. Zinc is especially important during periods of rapid growth, both pre- and postnatally, and for tissues with rapid cellular differentiation and turnover, such as the immune system and the gastrointestinal tract. Critical functions that are affected by zinc nutriture include pregnancy outcome, physical growth, susceptibility to infection, and neurobehavioral development, among others.

Pregnancy outcome

Reproductive functions that have been examined in relation to zinc status are the duration of pregnancy (including rates of spontaneous abortion); fetal growth; the timing, sequencing, and efficiency of labor and delivery; and the incidence of stillbirths and congenital malformations. This voluminous literature has been reviewed by several authors [18–25]. Although there are clear relationships between induced zinc deficiency and detrimental outcomes for each of these aspects of reproductive function in animal models [19, 21], especially when zinc deficiency is severe, the results of human studies have been less consistent, possibly due to small sample sizes, other inadequacies in study design, and the difficulty of accurately classifying individual zinc status. In some cases, zinc intervention trials were conducted in unselected women who were unlikely to be zinc deficient [26, 27], so negative results of these trials are not surprising. In almost all of the human trials, supplementation began no earlier than the second trimester of pregnancy, so there is very little information from humans on the effect of zinc nutriture during early pregnancy on pregnancy outcome.

In summary, there is considerable information from studies of animals with severe zinc deficiency and suggestive evidence from human observational studies and intervention trials to indicate that maternal zinc nutriture can influence several aspects of reproductive function and pregnancy outcome. Additional studies are needed of humans in different settings and under varied study conditions to define more precisely which women are likely to benefit from interventions to enhance their zinc status. Because of evidence from animal studies indicating that even a few days of low zinc intake at different stages of pregnancy can affect the outcome of pregnancy, human studies are needed in which supplemental zinc is provided throughout pregnancy, including the periconceptual period.

Morbidity

Research in zinc-deficient experimental animals has demonstrated dramatic changes in several components of the immune system, including lymphopenia, thymic atrophy, impaired cell-mediated immunity, and reduced antibody production. This body of work has been reviewed by Gershwin et al. [28], Shankar and Prasad [29], and Fraker et al. [30], among others. Considering the likely impact of these zinc-related abnormalities of immune function, a number of studies have been completed during the past few years to determine the effects of zinc supplementation on the incidence, and in some cases the severity and duration, of diarrhea, pneumonia, and malaria. To examine the consistency of results and to increase the statistical power of the individual studies, the results of the trials examining diarrhea and pneumonia outcomes have been pooled in several secondary analyses. The results of one pooled analysis indicate that continuous zinc supplementation produces substantial and consistent reductions in both diarrhea and acute lower respiratory infections [31]. In a separate set of pooled analyses, the effect of supplementary zinc supplied as an adjunct to other therapy was evaluated in children with acute or persistent diarrhea [32]. This analysis found that zinc supplements provided as adjunctive treatment of children with either acute or persistent diarrhea reduced the duration of illness and the risk of treatment failure. Because of the known negative association between diarrheal prevalence and growth velocity, it is conceivable that zinc therapy might also reduce the impact of these illnesses on growth. Limited information is also available on the effects of zinc supplementation on the risk of malaria. In two community-based trials, zinc-supplemented children made fewer clinic visits for malaria-attributable febrile episodes [33, 34].

Physical growth

The impact of zinc on growth was first described in humans in adolescent populations in Iran and Egypt [35, 36]. In these studies of young adults who presented with a syndrome characterized by varying degrees of growth stunting and delayed sexual maturation (hypogonadal dwarfism), treatment with zinc induced accelerated growth and commencement of sexual maturation in most participants [36, 37]. However, this response was not duplicated in a population of stunted and sexually delayed adolescents in a different area of Egypt [38], possibly because of other limiting nutrients in their diets.

In younger children, a total of 25 controlled clinical trials of the effect of zinc supplementation on growth were summarized in a recently completed meta-analysis [39]. Overall, there was a small, but highly significant, impact of zinc supplementation on children's height increments, with an average effect size of 0.22 SD. This effect was present for the subgroup of studies with mean initial height-for-age Z scores less than –2.0, but not for those with mean initial height-for-age Z scores greater than or equal to –2.0. The height response to zinc supplementation was unrelated to the dosage schedule employed and the duration of supplementation. Among studies with initially stunted children, the average effect size of zinc supplementation was moderately large, averaging 0.49 SD units. There was also a small, but highly significant, impact of zinc supplementation on children's weight increments, with an average effect size of 0.26 SD units. Interestingly, the effect of zinc supplementation on change in weight was negatively associated with mean initial plasma zinc levels. Among the subset of studies with low mean initial plasma zinc concentrations (< 80 μg/dl), the impact of zinc supplementation was moderately large. The effect of zinc supplementation on children's growth may be due to its direct impact on nucleic acid and protein synthesis [40] and hormonal mediators of growth [41], or its effects on appetite [42] or risk of infection, as discussed above [31]. On the basis of this extensive research experience, there seems to be strong evidence of a relationship between zinc deficiency and growth stunting. In those settings with high rates of stunting, underweight, low plasma zinc concentrations, or a combination of these factors, programs to enhance zinc status may be useful interventions to increase children's growth and decrease current rates of nutritional stunting.

Neurobehavioral development

As recently reviewed by Black [43] and Sandstead et al. [44], the results of multiple studies in experimental animals indicate that a broad range of neurobehavioral abnormalities can occur with zinc deficiency. For example, fetuses of zinc-deprived pregnant rats had neuronal degeneration and a reduction in brain size [45, 46], and the problem-solving ability of zinc-depleted adult rats was less than that of control animals [47]. Studies in prepubertal monkeys with moderate zinc restriction found lower spontaneous motor activity and reduced performance of tasks that required visual attention [48–50].

The results of studies of zinc deficiency or zinc supplementation in humans are less consistent, possibly due in part to the broad range of subjects observed and the research designs employed. Nevertheless, a number of zinc-related behavioral abnormalities have also been described in humans. These include reports of changes in mood, loss of affect and emotional lability, anorexia, dysfunction of smell and taste, irritability, and depression [51, 52]. In trials in young children and pregnant women, zinc supplementation resulted in increased motor development scores [53] and increased activity and/or responsiveness in young children or fetuses [54–57], including a significantly reduced need for assisted ventilation of newborns in one study [58]. Researchers generally agree that the mechanisms by which zinc deprivation induces behavioral changes are unclear, and further study is needed to determine at what stage zinc deficiency influences behavior, whether these effects are reversible, how long zinc supplementation is needed to prevent the risks, and whether zinc must be provided along with other limiting nutrients to be effective.

Dietary sources and bioavailability of zinc

In addition to the previously described effect of an individual's zinc status on zinc absorption, the total zinc content of the diet and the bioavailability of zinc from its food components also influence the efficiency of zinc absorption. Discounting the effect of zinc status, zinc absorption is determined largely by its solubility in the intestinal lumen, which in turn is affected by the chemical form of zinc and the presence of specific inhibitors and enhancers of absorption. The major inhibitor of zinc absorption is myoinositol hexaphosphate (phytate), which is present in many plant foods, especially cereals and legumes, and irreversibly binds zinc under conditions present in the intestinal lumen. Organs and flesh of mammals, fowl, fish, and crustaceans are the richest food sources of zinc, and these foods do not contain phytate; therefore, they are particularly good sources of absorbable zinc (table 1). Eggs and dairy products are also free of phytate, although they have a slightly lower zinc content than organs and flesh foods. Most cereals and legumes have an intermediate level of zinc, but their high phytate content reduces the amount of zinc available for absorption. When these staples are fermented (as occurs with leavened breads and with porridges prepared from fermented cereals), the fermenting organisms produce phytases that break down phytates, thus increasing the amount of absorbable zinc. Rice and starchy roots and tubers have lower zinc contents than legumes and cereals other than rice. For the most part, fruits and vegetables are not rich sources of zinc, although some green leafy vegetables, like spinach, have a fairly high zinc density, albeit of uncertain bioavailability.

To estimate the likely absorption of zinc from the mixed diet, a phytate-zinc molar ratio can be calculated as the phytate content of the foods/660 (the molecular weight (MW) of phytate) divided by the zinc content of the foods/65.4 (the molecular weight

TABLE 1. Zinc and phytate contents of different foods, and estimated amount of zinc available for absorption

Food group	Zn content		Phytate content		Absorbable Zn[a]
	mg/100 g	mg/100 kcal	mg/100 g	Phytate:zinc molar ratio	mg/100 g
Liver, kidney (beef, poultry)	4.2–6.1	2.7–3.8	0	0	2.1–3.1
Meat (beef, pork)	2.9–4.7	1.1–2.8	0	0	1.4–2.4
Poultry (chicken, duck, etc.)	1.8–3.0	0.6–1.4	0	0	0.9–1.5
Seafood (fish, etc.[b])	0.5–5.2	0.3–1.7	0	0	0.2–2.6
Eggs (chicken, duck)	1.1–1.4	0.7–0.8	0	0	0.6–0.7
Dairy (cow's milk, cheese)	0.4–3.1	0.3–1.0	0	0	0.2–1.6
Seeds, nuts (sesame, pumpkin, almond, etc.)	2.9–7.8	0.5–1.4	1760–4710	22–88	0.3–0.8
Bread (white flour, yeast)	0.9	0.3	30	3	0.4
Whole-grain cereal (wheat, maize, brown rice, etc.)	0.5–3.2	0.4–0.9	211–618	22–53	0.1–0.3
Beans, lentils (soy, kidney bean, chickpea, etc.)	1.0–2.0	0.9–1.2	110–617	19–56	0.1–0.2
Refined cereal grains (white flour, white rice, etc.)	0.4–0.8	0.2–0.4	30–439	16–54	0.1
Fermented cassava root	0.7	0.2	70	10	0.2
Tubers	0.3–0.5	0.2–0.5	93–131	3–27	< 0.1–0.2
Vegetables	0.1–0.8	0.3–3.5	0–116	0–42	< 0.1–0.4
Fruits	0–0.2	0–0.6	0–63	0–?	< 0.1–0.2

a. Amount of zinc available for absorption estimated as 45%–55% if phytate:zinc(P:Z) molar ratio < 5, and 30%–35% if P:Z = 5–15, 10–15% if P:Z > 15.
b. Excluding oysters.
Data sources: refs. 59–61.

of zinc). Phytate and zinc are usually reported in milligrams so the equation would be: (mg phytate/660 MW phytate)/(mg zinc/65.4 MW zinc). Information on the phytate content of various foods has been compiled in several databases [62–64]. It is generally considered that diets with a phytate-zinc molar ratio greater than 15 have relatively poor zinc bioavailability, those with a phytate-zinc molar ratio between 5 and 15 have medium zinc bioavailability, and those with a phytate-zinc molar ratio less than 5 have relatively good zinc bioavailability [65]. The relationship between zinc intake, the phytate-zinc molar ratio of the diet, and zinc absorption has been described by the World Health Organization (WHO) [65], which defined three categories of diets with high, medium, or low zinc availability, based on the proportion of energy from animal sources, the types of processing of cereals, the amounts of inorganic calcium salts, and the zinc:phytate molar ratio. WHO [65] estimates that about 45% to 55% of the element is absorbed from a high-bioavailability diet, 30% to 35% from a medium-bioavailability diet, and 10% to 15% from a low-bioavailability diet (fig. 1), depending on the zinc content of the meal and assuming a typical intake of approximately 3 to 5 mg per meal.

Based on her own and others' research, Sandström has recently summarized studies of the fractional and net absorption of zinc under different dietary conditions [66–77]. Zinc was absorbed most efficiently from aqueous solutions and from meals containing animal products. Absorption was considerably less from phytate-containing meals. Fortification of foods with exogenous zinc generally produced a small reduction in fractional absorption but had a positive impact on net absorption. However, fortification of foods with a high phytate:zinc molar ratio had only a small effect on net zinc absorption. Another approach to increasing the amount of zinc absorbable from high-phytate foods is to reduce the phytate content of these foods. Gibson et al. [78] reviewed the use of different food-processing methods, such as milling, soaking, and fermentation, to increase the bioavailability of zinc and other minerals, such as iron and calcium, from high-phytate staple foods. Specific practices that are compatible with local experience could be encouraged as an alternative or adjunct to other methods of increasing the availability of zinc. Because of remaining uncertainties in the estimates of zinc absorption from different diets by individuals of different zinc status, further work is needed to validate the ability of dietary data to predict zinc status.

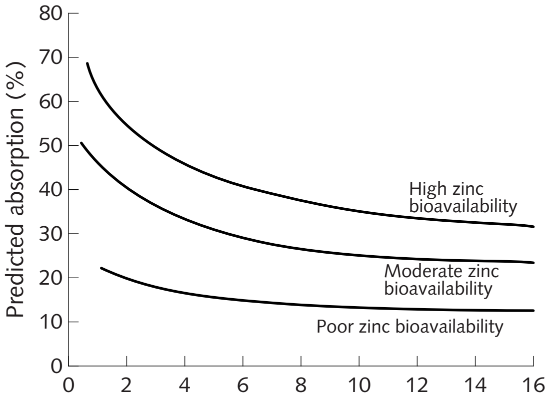

FIG. 1. Predicted fractional absorption of dietary zinc (%), according to level of zinc intake and zinc bioavailability in the diet. Data from World Health Organization [65]

Zinc requirements

Determining adequacy of zinc

Estimates of zinc requirements have been developed by several expert committees, including those convened by WHO [65], the National Research Council of the United States [79], and the Panel on Dietary Reference Values of the United Kingdom [80]. The WHO committee estimated the physiological zinc requirements of adults as the sum of the amounts needed for tissue growth, maintenance, metabolism, and replacement of endogenous losses. Because intestinal and urinary losses change in relation to zinc status, two separate estimates of these requirements were developed. The so-called basal requirements of 1.0 mg/day in adult males and 0.7 mg/day in adult females refer to the amounts needed to balance the aforementioned physiological requirements of individuals who are fully adapted to low zinc intakes. Because this level of intake leaves no reserve for adaptation to any further decrease in intake, the second estimate was developed to provide a greater margin of safety. This estimate, which is referred to as the "normative physiological requirement," accounts for the fact that zinc absorption must be about 40% greater to balance fecal and urinary losses in individuals who are not yet adapted to low intakes. Hence, the normative zinc requirement was set at 1.4 mg/day for adult men and 1.0 mg/day for adult women.

Once the normative zinc requirement is applied to a particular category of individuals, the dietary requirement must be adjusted to account for the estimated percentage of zinc absorption from the diet (dietary requirement = normative requirement/ % absorption from usual diet). The WHO committee further suggested that population dietary recommendations should be established at a level such that individuals who consume 2 SD less than the population average intake would be able to satisfy their normative requirement. This would assure that in populations with a mean intake at the recommended population level, nearly all individuals would be able to satisfy their zinc needs. The WHO committee assumed a coefficient of variation in dietary intake of 25% and therefore proposed that the population mean "normative dietary requirement" should be set at a level such that 50% (or 2 SD) less than this mean would be equivalent to the age- and sex-specific normative requirement. For example, if the normative requirement for adult men is 1.4 mg/day and the diet is of medium bioavailability (i.e., there is approximately 30% zinc absorption), then the normative dietary requirement is 1.4/0.3 = 4.7. The population mean dietary requirement is therefore set at 9.4 mg/day to assure that individuals who consume only 50% of the population mean dietary requirement would satisfy their normative dietary requirement.

In addition to the foregoing reasoning applied to adults, the estimates of zinc requirements for children take into consideration the amounts needed for accretion of newly formed tissue and the proportionately greater endogenous losses of zinc per unit body weight that occurs in children. To account for the latter phenomenon, the endogenous losses per unit of basal metabolic rate in adults (rather than per unit body weight) were applied to children. The population mean dietary requirements suggested by WHO are presented by age, sex, and physiological status in table 2. It should be noted that the WHO recommendations assume that a fully breastfed infant under six months of age is able to meet his or her zinc needs from breastmilk alone.

The US National Research Council similarly assumed that zinc requirements of adults could be established by measuring endogenous losses and adjusting this for the amount of zinc absorbed from the diet. However, the US recommendations considered only one level of zinc absorption from a mixed diet (20% of intake). The US recommendations are generally consistent with the WHO recommendations for a diet with low to medium zinc bioavailability. The UK recommendations applied a similar conceptual framework but assumed a single figure of 30% absorption from the diet. Hence, the estimated UK reference zinc intake is generally less than the US estimate and is consistent with the WHO estimate for a medium bioavailability diet.

Zinc toxicity

Zinc has a low toxicity, although acute symptoms of nausea, vomiting, diarrhea, fever, and lethargy may be observed when large (about 1 g) doses are consumed. When zinc intake exceeds physiological needs by reasonably small amounts, homeostasis can be maintained by increased endogenous fecal and urinary excretion. However, if excessive zinc intake continues for prolonged periods of time, absorption of other trace elements, especially copper and iron, can be impaired. For example, intakes of supplements providing 50 mg of zinc per day for six weeks produced changes in erythrocyte copper-zinc superoxide dismutase, an indicator of copper status [81, 82]. At higher doses of zinc (160–660 mg/day), anemia and changes in immune function and lipoprotein metabolism have been observed in addition to abnormal indices of copper status [83–86]. Further studies are needed to specify the level of zinc intake at which any undesirable effects on copper metabolism, hematologic indices, immune function, and lipoprotein metabolism begin to occur. Moreover, it needs to be determined whether the recommended upper limit of zinc intake should be modified when it is consumed with other foods of varied phytate content. There is also some evidence that adverse effects of zinc are more likely to occur when copper intakes are low, and a zinc:copper molar ratio of no more than 15 has been suggested [87, 88].

TABLE 2. Recommended population dietary zinc intakes to meet normative physiologic requirements according to population group, age, and estimated zinc bioavailability in the diet

	Dietary Zn bioavailability[a]		
Population/age (yr)	High	Medium	Low
Infants			
0–0.5[b]	—	—	—
0.5–1	3.3	5.6	11.1
Children			
1–3	3.3	5.5	11.0
3–6	3.9	6.5	12.9
6–10	4.5	7.5	15.0
Males			
10–12	5.6	9.3	18.7
12–15	7.3	12.1	24.3
15–18	7.8	13.1	26.2
18–60	5.6	9.4	18.7
Females			
10–12	5.0	8.4	16.8
12–15	6.1	10.3	20.6
15–18	6.2	10.2	20.6
18–60	4.0	6.5	13.1
Pregnant women[c]	6.0	10.0	20.0
Lactating women 0–5 mo	7.3	12.2	24.3
Lactating women ≥ 6 mo	5.8	9.6	19.2

a. See text for definitions of high-, medium-, and low-bioavailability diets.
b. Breastfed infants < 6 months of age are assumed to be able to satisfy zinc requirements from human milk only.
c. Mean for all trimesters.
Source: data from World Health Organization [65].

Assessment of zinc status

Several authors have reviewed the range of techniques that have been proposed for evaluating the zinc nutriture of individuals and populations [89–91]. Most researchers agree that efficient regulation of zinc homeostasis complicates the diagnosis of zinc deficiency and excess. There are no generally accepted, reliable biomarkers of individual zinc status. Only when zinc deficiency is relatively severe is it possible to detect changes in tissue zinc concentrations. For these reasons, the definitive diagnosis of zinc deficiency is usually based on a high index of suspicion (as motivated by low dietary intake and/or poor bioavailability of zinc and/or suggestive clinical signs, such as growth retardation, delayed sexual maturation, dermatitis, behavioral changes, and defects in immune function) and documentation of a functional response to zinc supplementation. Obviously, the need to conduct a therapeutic trial to identify a functional response to supplementation complicates the ability to diagnose zinc deficiency and increases the cost of this assessment, especially because several months may be needed to measure certain functional responses, such as physical growth, with confidence.

Of the alternative techniques that have been proposed for direct evaluation of a population's zinc status, the ones that seem most promising for field application are assessment of the adequacy of zinc intakes and measurement of the population's mean plasma zinc concentration.

Assessment of zinc status using plasma zinc

Use of the mean plasma zinc concentration to assess the zinc status of a population requires proper collection and processing of blood from a representative sample of the population and analysis of the zinc concentration in the plasma or serum. Despite the difficulties in interpreting the plasma zinc concentration of individual subjects, there are several pieces of evidence that suggest that the mean plasma zinc concentration of a group of individuals may provide useful information on the zinc status of the population from which that sample is derived. For example, when the zinc intake of groups of volunteer study subjects is severely restricted, the mean plasma zinc concentration diminishes within a fairly short period of time [6], although the decline in plasma zinc concentration is more subtle when zinc intake is only moderately restricted [17]. Nevertheless, results from a recent meta-analysis of zinc intervention trials indicate that the mean plasma zinc concentration of subjects in individual studies predicted the magnitude of the response in weight gain following zinc supplementation [39]. When the initial mean plasma zinc concentration was greater than about 80 µg/dl, there was no response to zinc supplementation. With decreasing plasma zinc concentrations, there was, in general, a progressively greater response to zinc. Moreover, almost all studies found a significant increase in the plasma zinc concentrations following supplementation, suggesting that this indicator could also be used to assess successful delivery of zinc supplements.

Assessment of zinc status using dietary intake data

Gibson and Ferguson [92] have prepared a manual describing a field-applicable method for determining the adequacy of dietary zinc (and iron) intakes in developing countries. Dietary assessment requires quantitative measurement of food intake from a representative sample of the population of interest, knowledge of the zinc content of these foods, and appraisal of the likely absorption of zinc from the mixed diets [93, 94]. Dietary intake can be assessed quantitatively by a number of different methods, the simplest of which for population assessment is a modified interactive 24-hour dietary recall [92, 94, 95]. Once the daily food intake is known, the total zinc intakes can be estimated by multiplying the amounts of each of the foods that are consumed by their zinc contents, as recorded in local food-composition tables or in databases available internationally, such as the US Department of Agriculture (USDA) food-composition database [61]. In developing countries, the World Food Dietary Assessment System can be used [59]. The nutrient database associated with this system contains food composition values for 1800 foods from six countries (Egypt, Kenya, Mexico, Senegal, India, and Indonesia) and provides data for 53 nutrients and antinutritional factors, including zinc, iron, dietary fiber, and phytate. Local databases are theoretically advantageous because the zinc content of foods can vary according to soil conditions, agronomic practices, and local food processing-techniques, although in many cases local food-composition tables contain fewer food items and fewer replicate analyses per item. Moreover, these local tables frequently omit analyses of zinc and/or phytic acid. To estimate the amount of zinc available for absorption from the diet, the diet can be categorized according to its phytate:zinc molar ratio, as described above.

Estimates of the global prevalence of zinc deficiency

Several authors have presented cogent arguments that zinc deficiency is likely to be widespread in low-income countries [96–98]. However, quantitative estimates of the percentage of the global population at risk of inadequate zinc nutriture and specific information on the prevalence of deficiency in particular settings are still lacking, in large part because of the aforementioned difficulties in assessing individual zinc status. This lack of information has been a major limiting factor in convincing policy makers of the need to develop programs to reduce the rate of zinc deficiency.

One indirect method that can be used for estimating global rates of zinc deficiency is analysis of previously collected information on the total daily per capita amount of zinc in the national food supply in relation to the population's theoretical zinc requirements, and a second indirect indicator to consider is a review of national rates of childhood stunting, as documented in the UNICEF report of the State of the World's Children [99]. These are described in the following paragraphs.

Zinc in the global food supply

Data on the amounts of major food commodities available for human consumption are listed for most countries in the food-balance sheets of the Food and Agriculture Organization (FAO) [60]. Despite the inherent weaknesses in this type of national-level statistics, the food-balance sheets provide reasonably reliable information on the total amounts and types of foods available in a broad range of countries. By calculating the amount of zinc present in these foods and the amounts that are potentially absorbable, as estimated from their phytate:zinc ratios, it is possible to assess whether the food supply is adequate to satisfy the population's theoretical requirements for zinc.

To estimate the zinc content of the global food supply, information was downloaded from the FAO food-balance sheets [60]. The food-balance sheets provide information on the annual amounts of 95 major food commodities that are available for human consumption in 178 different countries. The amount of zinc potentially available for absorption from these foods was also estimated by using WHO guidelines based on the phytate:zinc ratio (P:Z) of the food supply [65].

Table 3 displays regional data on the mean daily per capita availability of the following items in the food supply of 178 countries: total energy (kcal/day), total zinc (mg/day), zinc density (mg/1000 kcal), phytate (mg/day), P:Z molar ratio, estimated absorbable zinc (mg/day), and zinc as a percentage of the weighted average daily per capita zinc requirement. The regions are ranked in descending order according to the amount of absorbable zinc in the food supply. The mean daily per capita amount of zinc in the national food supply ranges from about 11 to 12 mg/day in the more affluent countries of Western Europe, North America, and the Western Pacific, to about 7 to 9 mg/day in the poorer regions of South and Southeast Asia, Northern Africa and Eastern Mediterranean, and sub-Saharan Africa. The zinc content of the national food supplies in China and Latin America is intermediate. The total zinc content of national food supplies is strongly associated with the total energy content the and percentage of energy provided by animal sources (data not shown). Notably, in the wealthier countries, more than half the zinc is provided by animal sources, as compared with 15% to 25% in the poorer countries, leading to sizable differences in the P:Z molar ratios among regions and approximately threefold differences in the estimated amount of zinc that is likely to be absorbed from the available foods (table 3). The food supply of Western Europe and North America provides about 150% of the weighted mean per capita normative population dietary requirement, whereas the food supply of South and Southeast Asia, Northern Africa and Eastern Mediterranean, and sub-Saharan Africa provides only about 50% to 60% of this requirement.

The percentage of the population at risk for inadequate intake was estimated for each country, as follows. The mean normative dietary requirement of zinc was assumed to be 50% of the WHO population dietary requirement, as calculated above, and was assumed to be fixed. The availability of food sources of zinc to individuals was assumed to follow a Gaussian distribution, with the standard deviation equal to 25% of the mean, as suggested by WHO [65]. The percentage of the population at risk was therefore calculated as the area under the normal curve to the left of the normative physiological requirement. According to this approach, the global food supply places nearly half the world's population at risk of low zinc intake (i.e., the national food supplies of the countries analyzed provide nearly half the people in the world with less than the weighted mean per capita normative dietary requirement of their respective countries). The percentage of the national population at risk for low zinc intake ranges from 1%–13% in countries of Europe and North America to 68%–95% in South and Southeast Asia, Africa, and the Eastern Mediterranean regions, and globally nearly half of the world's population is at risk for low zinc intake.

A number of weaknesses in this approach to estimating the global prevalence of zinc deficiency must be recognized. First, the estimates of the amount of zinc in the food supply are only as good as the information provided in the national food-balance sheets. Because the amount of zinc in national food supplies is strongly correlated with the total amount of food energy, any underestimates in the available food supply will result in overestimates of the number of individuals at risk of low intake, and vice versa. Second, the food-balance sheets provide national-level data, and no information is given on the distribution of the food supply among and within households. Although an assumption of a 25% coefficient of variation in population zinc intake

TABLE 3. Daily per capita amounts of energy, zinc, and phytate in the diets of people in 178 countries, according to region (mean + SD)[a]

Variable	W Europe	USA & Canada	E Europe	W Pacific	Latin America & Caribbean	China, including Hong Kong	SE Asia	Sub-Saharan Africa	N Africa & E Mediterranean	South Asia	All regions
No. of countries	20	2	27	13	35	2	10	46	17	6	178
Population (millions)	457	305	413	223	498	1262	504	581	342	1297	5882
Energy (kcal)	3410 ± 135	3546 ± 164	2971 ± 255	2902 ± 273	2743 ± 313	2743 ± 33	2556 ± 226	2203 ± 379	2806 ± 450	2351 ± 99	2706 ± 434
Zn (mg)	12.4 ± 1.3	12.2 ± 0.5	10.8 ± 1.3	11.8 ± 1.0	9.9 ± 2.0	10.9 ± 0.2	9.0 ± 0.9	9.3 ± 2.0	8.7 ± 1.6	7.6 ± 0.6	10.0 ± 2.0
Zn density (mg/1000 kcal)	3.6 ± 0.4	3.5 ± 0.1	3.6 ± 0.3	4.1 ± 0.3	3.6 ± 0.4	4.0 ± 0.1	3.5 ± 0.1	4.3 ± 0.8	3.1 ± 0.6	3.2 ± 0.2	3.6 ± 0.5
Phytate (mg)	1596 ± 391	1542 ± 58	1567 ± 211	2123 ± 444	2111 ± 808	2074 ± 36	2248 ± 586	2530 ± 645	2206 ± 524	2068 ± 263	2045 ± 504
Phytate:Zn ratio	13.2 ± 4.8	12.5 ± 0.1	14.5 ± 2.2	18.1 ± 4.7	21.1 ± 6.0	18.8 ± 0.6	24.5 ± 4.6	26.9 ± 3.7	25.1 ± 3.5	26.9 ± 1.7	21.3 ± 6.0
Absorbable Zn (mg)	3.2 ± 1.2	2.9 ± 0.1	2.1 ± 0.6	2.0 ± 1.2	1.5 ± 1.1	1.5 ± 0.2	1.1 ± 0.2	1.0 ± 0.2	1.0 ± 0.3	0.8 ± 0.1	1.5 ± 0.9
% requirement (adjusted for phytate content) ($n = 163$)	137 ± 46	122 ± 5	87 ± 22	88 ± 46	73 ± 43	69 ± 7	56 ± 7	59 ± 13	55 ± 12	47 ± 4	72 ± 34
Estimated % of population at risk for low Zn intake	8.0 ± 17.1	0.9 ± 0.2	12.8 ± 18.1	18.6 ± 16.3	45.8 ± 26.7	21.4 ± 1.5	71.2 ± 14.2	68.0 ± 25.9	73.5 ± 20.5	95.4 ± 2.1	48.9 ± 36.8

a. Analyses assume that wheat is consumed as 99% white flour (75% extraction) and 1% whole wheat, rice is consumed as white rice, and other cereals as whole grains. No assumptions are made with regard to fermentation of foods.

was employed, as suggested by WHO, if the actual variability in intake is greater than this, the current analyses would tend to underestimate the percentage of individuals at risk for low intake in countries with food zinc supplies above the requirement and overestimate the percentage of individuals at risk for low intake in countries with food zinc supplies below the requirement.

Third, the WHO estimates of age- and sex-specific normative physiological requirements assume that these are fixed, when in fact they vary among individuals. It is conceivable that some individuals might satisfy their physiological needs with lower zinc intakes. Finally, other possible flaws in this approach can result from inaccuracies in the food-composition database, failure to correct adequately for the effects of food processing on zinc and phytate contents, and uncertainties in the estimated physiological requirements for zinc and bioavailability of zinc from different diets. Also, it must be recognized that the total amount of food in the national food supply is almost certainly greater than the amounts actually consumed, and this difference between food availability and food consumption is probably greater in the more affluent countries. Notwithstanding the uncertainties in the estimates of the adequacy of zinc in national food supplies, the data do provide reasonable insights into the countries and regions that are likely to be at greatest risk for low intakes of absorbable zinc and consequent zinc deficiency.

Stunting

As mentioned, children with moderate to severe stunting respond to zinc supplementation more than children who are not stunted. Notably, those countries with high rates of stunting tend to be those with high risks of low zinc intake due to low availability of zinc in the food supply. Those countries also tend to have elevated rates of infant and child mortality, low birthweight, and postnatal malnutrition [99]. These relationships do not indicate causality, but they do suggest that high rates of stunting could be included as a possible indicator of zinc deficiency in the absence of more reliable indicators of zinc status.

Conclusions

Although there are no generally accepted biomarkers of zinc status, it is possible to use plasma zinc or consumption of dietary zinc (while considering the bioavailability of that zinc) in representative samples of the population as two relatively reliable methods of assessing zinc deficiency in those populations. However, these data are only available in a few countries throughout the world. National food-balance sheets are available from at least 178 countries, and the rates of stunting in children under five years of age are available in at least 163 countries worldwide. Therefore, these could be used as preliminary indicators of the risk of zinc deficiency until more appropriate data are available.

Based on the information presented above concerning the amount of zinc present in national food supplies, it appears that the risk of low dietary intake of absorbable zinc and consequent zinc deficiency are widespread problems affecting between one-third and one-half of the world's population. Zinc deficiency may induce a number of critical functional abnormalities, including impaired reproductive performance, depressed immune function and secondary increases in the incidence and severity of infections, growth failure and secondary nutritional stunting, and abnormalities of neurobehavioral development. Because of the likely high global prevalence of zinc deficiency and the serious range of complications that can be induced by this condition, public health programs are urgently needed to prevent low zinc intake and poor absorption of zinc.

References

1. Cousins RJ. Zinc. In: Ziegler EE, Filer LJ, Jr, eds. Present knowledge in nutrition. 7th ed. Washington, DC, USA: International Life Sciences Institute Press, 1996:293–306.
2. Prasad AS. Discovery of human zinc deficiency and marginal deficiency of zinc. In: Tomita H, ed. Trace elements in clinical medicine. Tokyo: Springer-Verlag, 1990:3–11.
3. Moynahan EJ. Acrodermatitis enteropathica: a lethal inherited human zinc-deficiency disorder. Lancet 1974;2:399–400.
4. Jackson MJ. Physiology of zinc: general aspects. In: Mills CF, ed. Zinc in human biology. London: Springer-Verlag, 1989:1–14.
5. King JC, Shames DM, Woodhouse LR. Zinc homeostasis in humans. J Nutr 2000;130:1360S–6S.
6. Baer MT, King JC. Tissue zinc levels and zinc excretion during experimental zinc depletion in young men. Am J Clin Nutr 1984;39:556–70.
7. Castillo-Duran C, Vial P, Uauy R. Trace mineral balance during acute diarrhea in infants. J Pediatr 1988;113:452–7.
8. Henry RW, Elmes ME. Plasma zinc in acute starvation. BMJ 1975;625–6.
9. Hambidge KM, Goodall MJ, Stall C, Pritts J. Post-prandial and daily changes in plasma zinc. J Trace Elem Electrolytes Health Dis 1989;3:55–7.
10. Smith KT, Failla ML, Cousins RJ. Identification of albumin as the plasma carrier for zinc absorption by perfused rat intestine. Biochem J 1978;184:627–33.
11. Cousins RJ. Systemic transport of zinc. In: Mills CF, ed. Zinc in human biology. London: Springer-Verlag, 1989:79–93.
12. Swanson CA, King JC. Reduced serum zinc concentration during pregnancy. Obstet Gynecol 1983;62:313–8.
13. Beisel WR, Pekarek RS, Wannemacher RW Jr. The impact of infectious disease on trace-element metabolism of the host. In: Hoekstra WG, Suttie J, Ganther H, Mertz W, eds. Trace element metabolism in animals 2. Baltimore, Md, USA: University Park Press, 1973: 217–40.
14. Falchuk KH. Effect of acute disease and ACTH on serum zinc proteins. N Engl J Med 1977;296:1129–34.
15. Brown KH. Effect of infections on plasma zinc concentration and implications for zinc status assessment in low-income countries. Am J Clin Nutr 1998;68:425S–39S.
16. Shenkin A. Trace elements and inflammatory response: implications for nutritional support. Nutrition 1995; 11:100–5.
17. Lukaski HC, Bolonchuk WW, Klevay LM, Milne DB, Sandstead HH. Changes in plasma zinc content after exercise in men fed a low-zinc diet. Am J Physiol 1984; 247:E88–E93.
18. Jameson S. Zinc and copper in pregnancy, correlations to fetal and maternal complications. Acta Med Scand 1976;593:5S–20S.
19. Hurley LS, Baly DL. The effects of zinc deficiency during pregnancy. In: Prasad AS, ed. Clinical, biochemical, and nutritional aspects of trace elements. New York: Alan R. Liss, 1982:145–59.
20. Apgar J. Zinc and reproduction. Annu Rev Nutr 1985; 5:43–68.
21. Keen CL, Hurley LS. Zinc and reproduction: effects of deficiency on foetal and postnatal development. In: Mills CF, ed. Zinc in human biology. London: Springer-Verlag, 1989:183–220.
22. King JC. Determinants of maternal zinc status during pregnancy. Am J Clin Nutr 2000;71:1334S–43S.
23. Tamura T, Goldenberg RL. Zinc nutriture and pregnancy outcome. Nutr Res 1996;16:139–81.
24. Caulfield LE, Zavaleta N, Shankar AH, Merialdi M. Potential contribution of maternal zinc supplementation during pregnancy to maternal and child survival. Am J Clin Nutr 1998;68:499S–508S.

25. Caulfield LE, Zavaleta N, Figueroa A, Leon Z. Maternal zinc supplementation does not affect size at birth or pregnancy duration in Peru. J Nutr 1999;129:1563–68.
26. Mahomed K, James DK, Golding J, McCabe R. Zinc supplementation during pregnancy: a double blind randomized controlled trial. BMJ 1989;299:826–30.
27. Jønsson B, Hauge B, Larsen MF, Hald F. Zinc supplementation during pregnancy: a double blind randomised controlled trial. Acta Obstet Gynecol Scand 1996;75:725–9.
28. Gershwin ME, Beach RS, Hurley LS. Trace elements: zinc. In: Nutrition and immunity. New York: Academic Press, 1985;204–20.
29. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. Am J Clin Nutr 1998;68(2 suppl):447S–63S.
30. Fraker PJ, King LE, Laakko T, Vollmer TL. The dynamic link between the integrity of the immune system and zinc status. J Nutr 2000;130:1399S–406S.
31. Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, Khatun F, Martorell R, Ninh NX, Penny ME, Rosado JL, Roy SK, Ruel M, Sazawal S, Shankar A (Zinc Investigators' Collaborative Group). Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. J Pediatr 1999;135:689–97.
32. Bhutta ZA, Bird SM, Black RE, Brown KH, Gardner JM, Hidayat A, Khatun F, Martorell R, Ninh NX, Penny ME, Rosado JL, Roy SK, Ruel M, Sazawal S, Shankar A (Zinc Investigators' Collaborative group). Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. Am J Clin Nutr 2000;72:1516–22.
33. Bates CJ, Evans PH, Dardenne M, Prentice A, Lunn PG, Northrop-Clewes CA, Hoare S, Cole TJ, Horan SJ, Longman SC, Stirling D, Aggett PJ. A trial of zinc supplementation in young rural Gambian children. Br J Nutr 1993;69:243–55.
34. Shankar AH, Genton B, Baisor M, Paino J, Tamja S, Adiguma T, Wu L, Rare L, Bannon D, Tielsch JM, West KP Jr, Alpers MP. The influence of zinc supplementation on morbidity due to *Plasmodium falciparu*m: a randomized trial in pre-school children in Papua New Guinea. Am J Hyg Trop Med 2000;62:663–9.
35. Prasad AS, Halsted JA, Nadimi M. Syndrome of iron deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism and geophagia. Am J Med 1961;31:532–46.
36. Prasad AS, Miale A, Farid Z, Sandstead HH, Schulert AR, Darby WJ. Biochemical studies on dwarfism, hypogonadism, and anemia. Arch Intern Med 1963;111:407–28.
37. Ronaghy HA, Caughey JE, Halsted JA. A study of growth in Iranian village children. Am J Clin Nutr 1968;21:488–94.
38. Carter JP, Grivetti LE, Davis JT, Nasiff S, Mansour A, Mousa WA, Atta AE, Patwardhan VN, Abdel Moneim M, Abdou IA, Darby WJ. Growth and sexual development of adolescent Egyptian village boys. Effects of zinc, iron, and placebo supplementation. Am J Clin Nutr 1969;22:59–78.
39. Brown KH, Peerson JM, Allen LH. Effect of zinc supplementation on children's growth: a meta-analysis of intervention trials. Bibliotheca Nutritio Dieta 1998;54:76–83.
40. MacDonald RS. The role of zinc in growth and cell proliferation. J Nutr 2000;130:1500S–8S.
41. Ninh NX, Thissen JP, Collette L, Gerard G, Khoi HH, Ketelslegers JM. Zinc supplementation increases growth and circulating insulin-like growth factor I (IGF-I) in growth-retarded Vietnamese children. Am J Clin Nutr 1996;63:514–9.
42. O'Dell BL, Reeves PG. Zinc status and food intake. In: Mills CF, ed. Zinc in human biology. London: Springer-Verlag, 1989:173–81.
43. Black M. Zinc deficiency and child development. Am J Clin Nutr 1998;68:464S–9S.
44. Sandstead HH, Frederickson CJ, Penland JG. History of zinc as related to brain function. J Nutr 2000; 130:496S–502S.
45. McKenzie JM, Fosmire GJ, Sandstead HH. Zinc deficiency during the latter third of pregnancy: effects on fetal rat brain, liver and placenta. J Nutr 1975;105:1466–75.
46. Prohaska JR, Luecke RW, Jasinski R. Effect of zinc deficiency from day 18 of gestation and/or during lactation on the development of some rat brain enzymes. J Nutr 1974;104:1525–31.
47. Caldwell DF, Oberleas D, Clancy JJ, Prasad AS. Behavioral impairment in adult rats following acute zinc deficiency. Proc Soc Exp Biol Med 1970;133:1417–21.
48. Golub MS, Gershwin ME, Hurley LS, Hendrickx AG, Saito WY. Studies of marginal zinc deprivation in rhesus monkeys: infant behavior. Am J Clin Nutr 1985;42:1229–39.
49. Golub MS, Takeuchi PT, Keen CL, Gershwin ME, Hendrickx AG, Lonnerdal B. Modulation of behavioral performance of prepubertal monkeys by moderate dietary zinc deprivation. Am J Clin Nutr 1994;60:238–43.
50. Golub MS, Takeuchi PT, Keen CL, Hendrickx AG, Gershwin ME. Activity and attention in zinc-deprived adolescent monkeys. Am J Clin Nutr 1996;64:908–15.
51. Aggett PJ. Severe zinc deficiency, In: Mills CF, ed. Zinc in human biology. London: Springer-Verlag, 1989;259–80.
52. Henkin RI, Patten BM, Re PK, Bronzert DA. A syndrome of acute zinc loss. Arch Neurol 1975;32:745–51.
53. Friel JK, Andrews WL, Matthew JD, Long DR, Cornel AM, Cox M, McKim E, Zerbe GO. Zinc supplementation in very-low-birth-weight infants. J Pediatr Gastroenterol Nutr 1993;17:97–104.
54. Ashworth A, Morris SS, Lira PIC, Grantham-McGregor SM. Zinc supplementation, mental development and behaviour in low birth weight term infants in northeast Brazil. Eur J Clin Nutr 1998;52:223–7.
55. Bentley ME, Caulfield LE, Ram M, Santizo MC, Hurtado E, Rivera JA, Ruel MT, Brown KH. Zinc supplementation affects the activity patterns of rural Guatemalan infants. J Nutr 1997;127:1333–8.
56. Merialdi M, Caulfield LE, Zavaleta N, Figueroa A, DiPietro JA. Adding zinc to prenatal iron and folate tablets improves fetal neurobehavioral development. Am J Obstet Gynecol 1998;180:483–90.
57. Sazawal S, Bentley M, Black RE, Dhingra P, George S, Bhan MK. Effect of zinc supplementation on observed activity in low socioeconomic Indian preschool chil-

dren. Pediatrics 1996;98:1132–7.

58. Cherry FF, Sandstead HH, Rojas P, Johnson LK, Batson KH, Wang XB. Adolescent pregnancy: associations among body weight, zinc nutriture, and pregnancy outcome. Am J Clin Nutr 1989;50:945–54.
59. Bunch S, Murphy SP. User's Guide to the operation of the World Food Dietary Assessment Program. Berkeley, Calif, USA: Office of Technology Licensing, University of California, 1994.
60. Food and Agriculture Organization. Food balance sheets, country averages 1990–1997. In: FAO statistical databases [databases online]. Available from http://apps.fao.org/lim500/nph-wrap.pl?FoodBalanceSheet&Domain=FoodBalanceSheet. Cited June–August 1999.
61. United States Department of Agriculture, Agricultural Research Service. USDA nutrient data-base for standard reference (release 13) [database online]. Beltsville, Md, USA: Nutrient Data Laboratory, USDA. Available from http://www.nal.usda.gov/fnic/cgi-bin/foodcomp/. Cited September 1999.
62. Oberleas D, Harland BF. Phytate content of foods: effect on dietary zinc bioavailability. J Am Diet Assoc 1981;79:433–6.
63. Oberleas D. Phytate content in cereals and legumes and methods of determination. Cereal Foods World 1983;28:352–7.
64. Reddy NR, Pierson MD, Sathe SK, Salunkhe DK. Phytates in cereals and legumes. Boca Raton, Fla, USA: CRC Press, 1989.
65. World Health Organization. Trace elements in human nutrition and health. Geneva: WHO, 1996.
66. Farah DA, Hall MJ, Mills PR, Russell RI. Effect of wheat bran on zinc absorption. Hum Nutr Clin Nutr 1984;38C:433–41.
67. Flanagan PR, Cluett J, Chamberlain MJ, Valberg LS. Dual-isotope method for determination of human zinc absorption: the use of a test meal of turkey meat. J Nutr 1985;115:112–22.
68. Lönnerdal B, Cederblad Å, Davidsson L, Sandström B. The effect of individual components of soy formula and cows' milk formula on zinc bioavailability. Am J Clin Nutr 1984;40:1064–70.
69. Nävert B, Sandström B, Cederblad Å. Reduction of the phytate content of bran by leavening in bread and its effect on zinc absorption in man. Br J Nutr 1985;53:47–53.
70. Sandström B, Almgren A, Kivistö B, Cederblad Å. Effect of protein level and protein source on zinc absorption in humans. J Nutr 1989;119:48–53.
71. Sandström B, Arvidsson B, Cederblad Å, Björn-Rasmussen E. Zinc absorption from composite meals. I. The significance of wheat extraction rate, zinc, calcium, and protein content in meals based on bread. Am J Clin Nutr 1980;33:739–45.
72. Sandström B, Cederblad Å. Zinc absorption from composite meals. II. Influence of the main protein source. Am J Clin Nutr 1980;33:1778–83.
73. Sandström B, Cederblad Å. Effect of ascorbic acid on the absorption of zinc and calcium in man. Int J Vitam Nutr Res 1987;57:87–90.
74. Sandström B, Davidsson L, Cederblad Å, Lönnerdal B. Oral iron, dietary ligands and zinc absorption. J Nutr 1985;115:411–4.
75. Sandström B, Davidsson L, Eriksson R, Alpsten M, Bogentoft C. Retention of selenium (75Se), zinc (65Zn) and manganese (54Mn) in humans after intake of a labelled vitamin and mineral supplement. J Trace Elem Electrolytes Health Dis 1987;1:33–8.
76. Valberg LS, Flanagan PR, Chamberlain MJ. Effects of iron, tin, and copper on zinc absorption in humans. Am J Clin Nutr 1984;40:536–41.
77. Brown KH, Wuehler SE, eds. Zinc and human health: results of recent trials and implications for program interventions and research. Ottawa: Micronutrient Initiative and International Development Research Centre, 2000.
78. Gibson RS, Hotz C, Temple L, Yeudall F, Mtitimuni B, Ferguson E. Dietary strategies to combat deficiencies of iron, zinc, and vitamin A in developing countries: development, implementation, monitoring, and evaluation. Food Nutr Bull 2000;21:219–231.
79. National Research Council. Recommended dietary allowances. 10th ed. Washington, DC: National Academy Press, 1989.
80. Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy. Dietary reference values for food energy and nutrients for the United Kingdom. London: Her Majesty's Stationery Office, 1991.
81. Fischer PWF, Giroux A, L'Abbe MR. Effect of zinc supplementation on copper status in adult man. Am J Clin Nutr 1984;40:743–6.
82. Yadrick MK, Kenney MA, Winterfeldt EA. Iron, copper, and zinc status: response to supplementation with zinc or zinc and iron in adult females. Am J Clin Nutr 1989;49:145–50.
83. Porter KG, McMaster D, Elmes ME, Love AHG. Anaemia and low serum-copper during zinc therapy. Lancet 1977;ii:774.
84. Chandra RK. Excessive intake of zinc impairs immune responses. JAMA 1984;252:1443–6.
85. Patterson WP, Winklemann M, Perry MC. Zinc-induced copper deficiency: megamineral sideroblastic anemia. Ann Intern Med 1985;103:385–6.
86. Hooper PL, Visconti L, Garry PJ, Johnson GE. Zinc lowers high-density lipoprotein-cholesterol levels. JAMA 1980;244:1960–1.
87. Davis CD, Milne DB, Nielsen FH. Changes in dietary zinc and copper affect zinc-status indicators of post-menopausal women, notably, extracellular superoxide dismutase and amyloid precursor proteins. Am J Clin Nutr 2000;71:781–8.
88. Sandstead HH. Requirements and toxicity of essential trace elements, illustrated by zinc and copper. Am J Clin Nutr 1995;61:621S–4S.
89. King JC. Assessment of zinc status. J Nutr 1990;120:1474–9.
90. Aggett PJ, Favier A. Zinc. Int J Vitam Nutr Res 1993;63:301–7.
91. Hambidge KM, Krebs N. Assessment of zinc status in man. Indian J Pediatr 1995;62:157–68.
92. Gibson RS, Ferguson EL. An interactive 24-hour recall for assessing the adequacy of iron and zinc intakes in developing countries. Washington, DC: International Life Sciences Institute Press, 1999.
93. Murphy S, Beaton GH, Calloway DH. Estimated mineral intakes of toddlers: predicted prevalence of inad-

equacy in village populations in Egypt, Kenya, and Mexico. Am J Clin Nutr 1992;56:565–72.
94. Gibson RS, Ferguson EL. Assessment of dietary zinc in a population. Am J Clin Nutr 1998;68:430S–4S.
95. Gibson RS. Principles of nutritional assessment. New York: Oxford University Press, 1990.
96. Sandstead HH. Zinc deficiency. A public health problem? Am J Dis Child 1991;145:853–9.
97. Shrimpton R. Zinc deficiency—Is it widespread but under-recognized? ACC/SCN News 1993;9:24–7.
98. Gibson RS. Zinc nutrition in developing countries. Nutr Res Rev 1994;7:151–73.
99. UNICEF. State of the world's children. New York: UNICEF, 1999.
100. United Nations. WISTAT—Women's indicators and statistics database of the United Nations [CD-ROM, version 3]. New York: United Nations Publications, 1994.

Zinc metabolism and requirements

Michael Hambidge and Nancy F. Krebs

Abstract

Current knowledge of the metabolism of zinc is summarized in relation to the clinical and public health importance of human zinc deficiency. Zinc metabolism is considered in relation to estimations of zinc requirements. Special attention is focused on the role and limitations of regulation of intestinal absorption of exogenous dietary zinc and of intestinal excretion of endogenous zinc in the maintenance of zinc homeostasis. The dynamic interrelationships between these variables and between each of these and readily exchangeable pools of body zinc are highlighted, as is the impact of dietary phytate on zinc requirements. Measurements of these variables utilizing zinc stable isotope techniques can provide quantitative information on zinc homeostasis and dietary zinc requirements in different communities, as well as facilitating assessment of alternative strategies for preventing zinc deficiency.

Biology of zinc

It is necessary to have some appreciation of the ubiquitous, versatile biology of zinc, if we are to understand how and why human zinc deficiency causes such a plethora of adverse effects involving multiple organ systems, which are nonspecific but of manifest public health importance.

Zinc has an outstanding ability to form strong, but readily exchangeable and flexible, ligands with organic molecules, including proteins and nucleic acids [1]. To a large measure, this ability undoubtedly underlies the incorporation of this micronutrient into so many basic cellular metabolic processes. Notable among these is the role of zinc at the catalytic site of a diverse range of metalloenzymes. The tertiary structure of many proteins is determined by zinc ligands. Thus, the integrity of cell membranes and of some ion channels is zinc-dependent. One notable example of the structural roles of this metal is the "zinc finger protein" [2], which is the most common motif for those processes of transcription factors that link with the double helix of DNA to initiate gene expression, and which is also essential, for example, for the tertiary structure of nuclear receptors for steroid hormones. It is now apparent that the expression of certain genes is modulated by the quantity of zinc ingested and absorbed [3]. Moreover, there is some evidence to support the hypothesis that the zinc ion can serve in an intracellular regulatory capacity, including regulation of cellular growth and differentiation.

Many of the wide range of zinc-dependent metabolic processes are required by all cells. This can explain why the consequences of zinc deficiency are so many and varied and also why they are nonspecific. The special importance of zinc during periods of rapid prenatal and postnatal growth and for systems such as the immune system, in which cells have such rapid turnover, is likely to be attributable in substantial part to the multiple roles of this micronutrient in cellular growth and differentiation.

It is also appreciated, however, that other zinc-dependent biology is organ- or system-specific, e.g., the role of this metal in neuronal transmission in the central nervous system [4].

Zinc metabolism and homeostasis

Discussion of zinc metabolism will focus on those aspects that are especially relevant to better understanding of dietary zinc requirements. Ultimately, of course, it is the effects of suboptimal zinc on zinc metabolism at a subcellular level that are most directly relevant to the clinical and public health consequences of zinc deficiency. Recent progress at the molecular and subcellular level has been substantial [5], as has progress in the identification of some of the zinc transporters that undoubtedly have a vital role in

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maintaining zinc homeostasis at a molecular level [6]. Currently, however, this progress is not at the point at which it can assist to a significant extent with quantitative estimates of dietary zinc requirements. This discussion will be limited, therefore, to selected aspects of human zinc metabolism at an organ-system and whole-body level. Lest this be interpreted as a temporary stopgap approach, the durable value of quantitative data on human zinc homeostasis at the whole-body level merits emphasis [7].

The application of zinc isotope tracer techniques combined with model-based compartmental analysis has served to illustrate the complexity of human zinc metabolism [8, 9]. As much as 90% of the 1.5 to 2 g of zinc in an adult man is present in slowly exchanging pools located principally in muscle and bone. Although these slowly turning-over zinc compartments are important to the organ systems in which they are located, as well as to total body zinc homeostasis, it is the approximately 10% of zinc that turns over rapidly, i.e., exchanging with zinc in plasma within a period of three days, that is thought to be especially important for so many aspects of zinc-dependent biology. Moreover, this exchangeable zinc pool, or rather combination of multiple pools, which encompasses zinc in the liver, pancreas, and other viscera, including the gastrointestinal tract (except for the luminal contents), is particularly sensitive to changes in the quantity of zinc ingested and absorbed [10].

The gastrointestinal tract has a predominant role in maintaining total body zinc homeostasis. In addition to providing partial regulation of the absorption of exogenous dietary zinc, the intestine is the major route for excretion of endogenous zinc. Moreover, it appears to be the only significant site at which there is regulation of the quantity of endogenous zinc excreted except in circumstances of severely restricted intake. It is only in these circumstances of severely restricted intake that there is measurable reduction in the quantity of zinc excreted via the kidneys [11–14], skin, and in the case of adult men, semen [13]. Over a broad physiological range of intake, i.e., from about 4 mg of zinc per day up to 15 to 20 mg of zinc per day in an adult man, these nonintestinal losses of endogenous zinc can be regarded as a constant. In contrast, there is a strongly positive correlation between the quantity of zinc absorbed and the quantity of endogenous zinc excreted in the feces over this same range of intake.

Current data are consistent with the concepts listed below.

Absorption of exogenous dietary zinc

The relative importance of regulation of absorption in maintaining zinc homeostasis is still unclear, but, at least in the short term, it appears to have a major role [14, 15]. In special physiologic circumstances, this may be of predominant importance in maintaining homeostasis. For example, the increase in fractional absorption of exogenous dietary zinc in early human lactation can be of sufficient magnitude to largely offset the quantity of zinc secreted by the mammary gland [16]. However, restrictions of dietary zinc intake to levels well below those that are habitual are not entirely offset by increases in fractional absorption. Moreover, short-term adaptive changes in zinc absorption in response to dietary zinc restriction are not necessarily maintained [17, 18].

The latter observations are consistent with data suggesting that the regulation of absorption of exogenous dietary zinc is not sufficient to maintain a constant size for at least some of the rapidly exchangeable zinc pools [19–21].

Considering the other side of the coin, the progressive decrease in fractional absorption of zinc in response to progressive increases in intake, while substantial, is insufficient to avert potentially large increases in the quantity of zinc absorbed with excessive intake [9, 22]. This suggests that caution is required in selecting quantities of zinc supplements, especially if these are intended for long-term use.

Dietary factors may have a major impact on the regulation of zinc absorption by increasing or decreasing the quantity of zinc in the small intestinal lumen that is available for absorption. Most notable among these factors is phytic acid, high intakes of which are the rule rather than the exception in individuals who, and populations that, depend on plant sources for their nutrient requirements [23].

Intestinal excretion of endogenous zinc

Large quantities of zinc are secreted into the gut lumen postprandially [24, 25], and the majority of this zinc is subsequently reabsorbed. It is likely that the processes of secretion and reabsorption are both regulated and have important roles in zinc homeostasis. Although measurement of these processes separately poses formidable challenges, the net outcome, i.e., the quantity of endogenous zinc excreted in the feces, can be and is now being measured, primarily as a result of recent advances in the application of zinc stable isotope techniques [7, 26]. These measurements, though still in their infancy, are adding to our quantitative understanding of zinc homeostasis and are a vital component of future human research aimed at unraveling the many unanswered questions about why and in what circumstances zinc deficiency occurs.

The relationship between absorbed zinc and intestinal excretion of endogenous zinc is never static. Even at low levels of zinc absorption, the more zinc absorbed, the greater the intestinal excretion of zinc and vice versa [20, 26, 27]. These observations are not consistent with the concept of a static obligatory quantity of endogenous zinc that is unavoidably excreted by the intestine, but rather are consistent with the concept of a constantly changing amount that is closely related to the quantity absorbed.

When absorption is low, compensatory decreases in the quantity of endogenous zinc excreted via the intestine have a major role in maintaining zinc homeostasis. Indeed, with long-term [18] or habitual [20] low zinc intake, intestinal regulation of endogenous zinc excretion appears to be the only effective homeostatic mechanism in some circumstances. It is important to note, however, that balance may only be achieved through this mechanism after some depletion of body zinc, most readily detected by diminution of more rapidly exchangeable zinc pools [20, 28].

As is the case with absorption, both host [19, 29] and dietary factors may have an adverse effect on the role of intestinal regulation of excretion of endogenous zinc in maintaining zinc homeostasis. Most notable of the host factors on a global basis is diarrhea [30], whereas phytate [31] is the most notable of the dietary factors.

The subtleties of the interrelationships between absorption of exogenous dietary zinc, intestinal excretion of endogenous zinc, and systemic zinc metabolism (especially that of rapidly exchanging pools) can now be explored quantitatively in diverse population groups, including young children, by using stable isotope techniques. A substantial increase in research in this area could provide the information needed to better understand zinc requirements and the practical limitations of zinc homeostasis.

Dietary zinc requirements

Recognition of the global public health importance of human zinc deficiency, especially in young children, is attributable in large measure to the results of multiple well-designed intervention studies with zinc supplements, many of which have been completed within the past decade [32, 33]. Increases in growth velocity have been one frequent result of these interventions. Although not universally observed, careful and repeated meta-analyses of these studies have confirmed that overall both weight gain and linear growth velocity have been significantly greater in the zinc-supplemented children than in those who received a placebo [32]. Apart from any beneficial effects on growth itself, full evaluation of which may require longer-term studies, it is relevant to emphasize that zinc has no pharmacologic effect on growth velocity [34]. Therefore, it is reasonable to conclude that a measurable growth response in well-designed and executed, placebo-controlled studies of zinc supplementation provides prima facie evidence of a preexisting growth-limiting zinc deficiency state. It is intuitively unlikely that some responses to zinc supplements result from correction of an underlying deficiency state, whereas others are the result of a pharmacologic effect. It is, therefore, reasonable to conclude that other documented effects of these intervention studies [33, 35] are also attributable to correction or prevention of zinc deficiency. This conclusion is also consistent with what is known about the pathophysiology of zinc deficiency.

This conclusion, in turn, has important implications for better understanding of human dietary zinc requirements under a range of host and dietary circumstances. Unfortunately, with only few exceptions, especially in studies undertaken in developing countries, these investigations have not included reported dietary data. Such data could, at the very least, enhance understanding of critical levels of intake under different host and environmental, especially dietary, circumstances in which evidence of zinc deficiency occurred. Such data would be very useful in refining intervention strategies to prevent the public health consequences of zinc deficiency.

Theoretically, there are at least six strategies that could be used to assist in the estimation of dietary zinc requirements.

Perhaps the simplest strategy, but one that lacks precision, is *estimating habitual intakes in populations without evidence of zinc deficiency*. This approach can, of course, also be inaccurate if subtle evidence of deficiency is overlooked.

Use of biomarkers of zinc status. Currently, available biomarkers of zinc status lack sufficient sensitivity to be more than of minor supportive value [36].

Utilization of functional indices of zinc deficiency. All potential indices identified lack specificity and are only of potential utility when combined with the following strategy.

Combination of baseline dietary intake data with results of zinc supplementation. As noted above, though potentially very useful, such data are currently very limited. There are, however, sufficient data, both positive and negative, available from the United States [37–39], Canada [40], and Chile [41, 42] to be of at least supportive value in estimating dietary zinc requirements for children fed diets in which the zinc is likely to be of moderate or high bioavailability.

Zinc balance data. Our review of published data for adult men suggests that the inherent inaccuracies in the balance technique have been sufficient to negate any theoretical utility of this approach. The theoretical value of this approach has also been denied on physiologic grounds [43], although this conclusion may merit careful reevaluation as more data on zinc homeostasis become available.

Factorial approach. This approach is based on determination of the minimal quantity of absorbed zinc that is required to match endogenous excretion of zinc via all routes. In addition, it must include the quantity of absorbed zinc required for new tissue in growing children and during the reproductive cycle. Once the requirement for absorbed zinc has been determined, calculation of the quantity of dietary zinc required will depend on measurement or estimation of fractional absorption.

Despite the limited data available at this time, the last approach offers the most useful strategy for estimating requirements. This paper will not include details of requirements calculated primarily utilizing this approach, but these should be available from the Food and Nutrition Board of the Institute of Medicine (USA) in the near future. Meanwhile, some important physiologic concepts about requirements that appear to be valid, based on detailed review of existing published data, are considered briefly in the remainder of this section.

Minimization of losses of endogenous zinc via all routes at very low zinc intakes ensures that, in the absence of other factors, such as high phytate intakes, net losses of body zinc are only modest and gradual [11, 12, 14]. These observations should not, however, be interpreted to mean that zinc requirements are very low and that "just a little more zinc" above these negligible intakes will meet requirements.

As absorbed zinc increases from these very low levels, urinary and integumental losses rapidly increase to a plateau that is not then exceeded in normal circumstances unless zinc supplements are administered. Simultaneously there is a progressive increase in intestinal excretion of endogenous zinc that correlates with the increase in absorbed zinc and does not plateau within a physiologic range of intake. Thus, although the rate of increase in absorbed zinc exceeds the rate of increase in intestinal excretion of endogenous zinc as the intake of available zinc increases, the increased intake has to be quite substantial before absorbed zinc "catches up" with total endogenous losses (and, in children, provides sufficient retention for new tissue requirements).

Alhough net zinc losses at intakes less than requirements are likely to be modest, they may also be cumulative, as complete adaptation appears not to occur. Functional disturbances can occur with almost undetectable diminution of tissue zinc levels. The young child is now well identified as a subgroup of the population at special risk from these insidious zinc-deficiency states.

The revised estimates of requirements (EARs or estimated average requirements) published by the Food and Nutrition Board of the Institute of Medicine are based primarily on meals in which the availability of zinc is relatively favorable [44]. This does not apply to the majority of developing countries. In recognition of the huge global issue of poor zinc bioavailability, due primarily to high phytate intakes, the World Health Organization (WHO) has published estimates of zinc requirements based on high, average, or low bioavailability [45]. It should be appreciated, however, that most existing quantitative human data on the effects of phytate are derived from single test meal data and do not provide information on effects other than those on absorption of exogenous zinc and do not provide insights into sustained long-term effects of high-phytate diets.

Infants and children

The preceding discussion of key variables of zinc homeostasis and their interrelationships and of how quantitative data on these can provide the basis for a factorial approach to estimating zinc requirements has given no attention to the effects of age and sex. Two groups of special concern are pregnant women [46, 47] and young children. Pregnancy has been covered elsewhere [48], but infants and young children require special consideration here.

Fully breastfed infants typically acquire adequate zinc from human milk, probably together with some contribution from neonatal stores, for the first six months of postnatal life [27]. Small-for-gestational age infants may be an exception to this statement [49, 50], possibly because of their diminished neonatal zinc stores (although this has not been proven). Premature infants fed their own mother's milk, and especially very-low-birthweight premature infants, either require or are likely to benefit from additional zinc after the first two months [51]. The favorable situation during the first six months for term infants is potentially in jeopardy if the mother's milk supply is low or if other fluids or complementary foods are given.

After six months, older breastfed infants are dependent on complementary foods for a substantial part of their zinc requirements, and as for iron, this is a stage of special concern with respect to zinc nutriture. From this stage through childhood, an approximate estimate of requirements can be derived from dietary data included in zinc intervention studies that have demonstrated a positive growth response (see above). However, as for adults, a factorial approach for older infants and children probably offers the best option at this time. Although estimates of requirements for older infants and children based on a factorial approach have been published recently [52], it should be appreciated that factorial calculations for the period between six months of age and adulthood are dependent on extrapolations from adult data. These data may be augmented or modified by data from younger infants [26, 53]. The acquisition of data for fractional absorption of zinc and intestinal excretion of endogenous zinc in older infants and young children is an especially high priority. In applying a factorial approach to children, retention required for growth has to be considered. Probably the best estimate available is that derived from chemical analysis of the whole body [54], which gives an average figure of approximately 20 mg per kilogram of new tissue.

Conclusions and implications for program-linked research

Our increased understanding of the biology of zinc leaves no reason to doubt the exceptional importance of zinc in human nutrition and public health. Although determining the specific biochemical and pathophysiological correlates of the clinical features of human zinc deficiency still requires much research, the ubiquity of zinc in biology and the roles of this metal in so many aspects of metabolism, including those that are central to cellular growth and differentiation, are very compatible with the wide variety of problems that have been linked with zinc deficiency. These include problems that are of substantial public health concern in the developing world.

Regulation of intestinal absorption of exogenous dietary zinc and of intestinal excretion of endogenous zinc has a preeminent role in maintaining zinc homeostasis. Although the combined regulation of these processes mitigates the effects of inadequate intake of bioavailable zinc in normal circumstances, adaptation appears to be less than perfect. We recognize this especially because of the extensive documentation of clinically important sequelae of suboptimal dietary zinc intake, despite reductions in tissue zinc that are frequently too small to detect. Supportive evidence has been derived from estimates of the size of exchangeable zinc pools and the typically positive correlation between these and the quantity of zinc ingested and absorbed.

Furthermore, on a global basis, dietary factors—notably phytic acid—are likely to reduce, sometimes greatly reduce, the quantity of ingested zinc that is available for absorption. This not only increases the risk of zinc deficiency, but also complicates the challenge of determining dietary requirements for this micronutrient. Similar considerations apply to certain host factors, notably diarrhea.

Fortunately, quantitative measurements of these variables under a variety of environmental and host circumstances are now feasible with the application of zinc stable isotope methodology. At this stage, application of these techniques should be combined with operational research designed to prevent (or treat) zinc deficiency at a community level. They should be used not only as a potent tool to help design optimal strategies for specific communities, but also to provide a quantitative means of evaluating the efficacy of these strategies.

References

1. Williams RJP. An introduction to the biochemistry of zinc. In: Mills CF, ed. Zinc in human biology. Berlin: Springer-Verlag, 1989:15–31.
2. Berg JM, Shi Y. The galvanization of biology: a growing appreciation for the roles of zinc. Science 1996;271:1081–5.
3. Cousins RJ. Nutritional regulation of gene expression. Am J Med 1999;106:20S–3S; discussion 50S–1S.
4. Frederickson CJ, Suh SW, Silva D, Frederickson CJ, Thompson RB. Importance of zinc in the central nervous system: the zinc-containing neuron. J Nutr 2000; 130:1471S–83S.
5. Hambidge KM. Zinc and health: current status and future directions. J Nutr 2000;130:1341S–3S.
6. McMahon RJ, Cousins RJ. Mammalian zinc transporters. J Nutr 1998;128:667–70.
7. Hambidge KM, Krebs NF, Miller L. Evaluation of zinc metabolism with use of stable-isotope techniques: implications for the assessment of zinc status. Am J Clin Nutr 1998;68:410S–3S.
8. Miller LV, Krebs NF, Hambidge KM. Human zinc metabolism: advances in the modeling of stable isotope data. In: Clifford AJ, Mueller HG, eds. Mathematical modeling in experimental nutrition. Advances in experimental medicine and biology. New York: Plenum Press, 1998;68:4145–7.
9. Wastney ME, Aamodt RL, Rumble WF, Henkin RI. Kinetic analysis of zinc metabolism and its regulation in normal humans. Am J Physiol 1986;251:R398–408.
10. Chesters JK. Metabolism and biochemistry of zinc. In: Prasad AS, ed. Clinical, biochemical, and nutritional aspects of trace elements. New York: Alan R. Liss 1982;221–38.
11. Baer MT, King JC. Tissue zinc levels and zinc excretion during experimental zinc depletion in young men. Am J Clin Nutr 1984;39:556–70.
12. Hess FM, King JC, Margen S. Zinc excretion in young women on low zinc intakes and oral contraceptive agents. J Nutr 1977;107:1610–20.
13. Johnson PE, Hunt CD, Milne DB, Mullen LK. Homeostatic control of zinc metabolism in men: zinc excretion and balance in men fed diets low in zinc. Am J Clin Nutr 1993;57:557–65.
14. Taylor CM, Bacon JR, Aggett PJ, Bremner I. Homeostatic regulation of zinc absorption and endogenous losses in zinc-deprived men. Am J Clin Nutr 1991;53:755–63.
15. Wada L, Turnland JR, King JC. Zinc utilization in young men fed adequate and low zinc intakes. J Nutr 1985;115:1345–54.
16. Lei S, Krebs NF, Westcott J, Li F, Miller L, Hambidge KM. Zinc (Zn) homeostasis during early lactation in women with low dietary Zn intakes. FASEB J 2000; 14:A476.

17. Johnson PE, Hunt JR, Ralston NVC. The effect of past and current dietary Zn intake on Zn absorption and endogenous excretion in the rat. J Nutr 1988;118:1205–9.
18. Lee D, Prasad AS, Hydrick-Adair C, Brewer G, Johnson PE. Homeostasis of zinc in marginal human zinc deficiency: role of absorption and endogenous excretion of zinc. J Lab Clin Med 1993;122:549–6.
19. Krebs KF, Westcott JE, Arnold TD, Kluger BM, Accurso FJ, Miller LV, Hambidge KM. Abnormalities in zinc homeostasis in young infants with cystic fibrosis. Pediatr Res 2000;48:256–61.
20. Lei S, Xiang M, Miller LV, Krebs NF, Lei T, Hambidge KM. Zinc absorption and intestinal losses of endogenous zinc in young Chinese women with marginal zinc intake. Am J Clin Nutr 1996;63:348–53.
21. Miller LV, Hambidge KM, Naake VL, Hong Z, Westcott JL, Fennessey PV. Size of the zinc pools that exchange rapidly with plasma zinc in humans: alternative techniques for measuring and relation to dietary zinc intake. J Nutr 1994;124:268–76.
22. Jackson MJ, Jones DA, Edwards RHT, Swainback IG, Coleman ML. Zinc homeostasis in man: studies using a new stable isotope-dilution technique. Br J Nutr 1984; 51:199–208.
23. Gibson RS. Zinc nutrition in developing countries. Nutr Res Rev 1994;7:151–73.
24. Matseshe JW, Phillips SF, Malagelada JR, McCall JT. Recovery of dietary iron and zinc from the proximal intestine of healthy man: studies of different meals and supplements. Am J Clin Nutr 1980;33:1946–53.
25. Krebs NF, Westcott JE, Huffer JW, Miller LV. Absorption of exogenous zinc and secretion of endogenous zinc in human small intestine. FASEB J 1998;12:A345.
26. Krebs NF, Miller LV, Naake VL, Lei S, Westcott JE, Fennessey PV, Hambidge KM. The use of stable isotope techniques to assess zinc metabolism. J Nutr Biochem 1995;6:292–307.
27. Krebs NF, Reidinger CJ, Miller LV, Hambidge KM. Zinc homeostasis in breastfed infants. Pediatr Res 1996; 39:661–5.
28. Krebs NF, Westcott JE, Miller LV, Herrmann TS, Hambidge KM. Exchangeable zinc (Zn) pool (EZP) size in normal infants: correlates with parameters of Zn homeostasis. FASEB J 2000;14:A205.
29. Ruz M, Solomons NW. Mineral excretion during acute, dehydrating diarrhea treated with oral rehydration therapy. Pediatr Res 1990;27:170–5.
30. Hambidge KM. Zinc and diarrheal disease in young children. Acta Paediatr Suppl 1992;381:82–6.
31. Turnlund JR, King JC, Keyes WR, Gong B, Michel MC. A stable isotope study of zinc absorption in young men: effects of phytate and cellulose. Am J Clin Nutr 1984;40:1071–7.
32. Brown KH, Peerson JM, Allen LH. Effect of zinc supplementation on children's growth: a meta-analysis of intervention trials. Bibl Nutr Dieta 1998;54:76–83.
33. Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, Khatun F, Martorell R, Ninh NX, Penny ME, Rosado JL, Roy SK, Ruel M, Sazawal S, Shankar A (Zinc Investigators' Collaborative Group). Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. J Pediatr 1999;135:689–97.
34. Williams RB, Mills CF. The experimental production of zinc deficiency in the rat. Br J Nutr 1970;24:989–1003.
35. Sandstead HH, Penland JG, Alcock NW, Dayal HH, Chen XC, Li JS, Zhao F, Yang JJ. Effects of repletion with zinc and other micronutrients on neuropsychologic performance and growth of Chinese children. Am J Clin Nutr 1998;68:470S–5S.
36. Hambidge KM, Krebs NF. Assessment of zinc status in man. Indian J Pediatr 1995;62:169–80.
37. Hambidge KM, Chavez MN, Brown RM, Walravens PA. Zinc nutritional status of young middle-income children and effects of consuming zinc-fortified breakfast cereals. Am J Clin Nutr 1979;32:2532–9.
38. Walravens PA, Krebs NF, Hambidge KM. Linear growth of low income preschool children receiving a zinc supplement. Am J Clin Nutr 1983;38:195–201.
39. Walravens PA, Hambidge KM, Koepfer DM. Zinc supplementation in infants with a nutritional pattern of failure to thrive: a double-blind, controlled study. Pediatrics 1989;83:532–8.
40. Gibson RS, Smit Vanderkooy PD, MacDonald AC, Goldman A, Ryan BA, Berry M. A growth-limiting, mild zinc-deficiency syndrome in some Southern Ontario boys with low height percentiles. Am J Clin Nutr 1989;49:1266–73.
41. Castillo-Duran C, Heresi G, Fisberg M, Uauy R. Controlled trial of zinc supplementation during recovery from malnutrition: effects on growth and immune function. Am J Clin Nutr 1987;45:602–8.
42. Castillo-Duran C, Garcia H, Venegas P, Panteon E, Torrealba I, Concha N. Zinc supplementation increases growth velocity of male children and adolescents with short stature. Acta Paediatr 1994;83:833–7.
43. Mertz W. Use and misuse of balance studies. J Nutr 1987;117:1811–3.
44. Food and Nutrition Board. Dietary reference intakes. Zinc. In: Vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. Washington, DC: Food and Nutrition Board, Institute of Medicine, 2000: 12–1 to 12–47.
45. World Health Organization. Zinc: deficiency and toxicity. In: Trace elements in human nutrition and health. Geneva: WHO, 1996:72–3.
46. Caulfield LE, Zavaleta N, Shankar AH, Merialdi M. Potential contribution of maternal zinc supplementation during pregnancy to maternal and child survival. Am J Clin Nutr 1998;68:499S–508S.
47. Merialdi M, Caulfield LE, Zavaleta N, Figueroa A, DiPietro J. Adding zinc to prenatal iron and folate tablets improves fetal neurobehavioral development. Am J Obstet Gynecol 1999;180:483–90.
48. King JC. Determinants of maternal zinc status during pregnancy. Am J Clin Nutr 2000;71(suppl):1334S–43S.
49. Castillo-Duran C, Rodriguez A, Venegas G, Alvarez P, Icaza G. Zinc supplementation and growth of infants born small for gestational age. J Pediatr 1995;127:206–11.

50. Sazawal S, Black RE, Menon VP, Dhingra U, Dhingra P, Mazumder S, Caulfield L, Khosla S. Effect of zinc and mineral supplementation in small for gestational age infants on growth and mortality. FASEB J 1999;13:A376.
51. Krebs NF. Zinc transfer to the breastfed infant. J Mammary Gland Biol Neoplasia 1999;4:259–67.
52. Brown K, Dewey K, Allen L. Complementary feeding of young children in developing countries: a review of current scientific knowledge. Geneva: World Health Organization, Programme of Nutrition, 1998.
53. Abrams SA, Wen J, Stuff JE. Absorption of calcium, zinc and iron from breast milk by five- to seven-month-old infants. Pediatr Res 1997;41:384–90.
54. Widdowson EM, Dickerson JWT. Chemical composition of the human body. In: Comar CL, Bronner F, eds. Mineral metabolism. An advanced treatise. Vol 2: The elements, Part A. New York: Academic Press, 1964:1–220.

Diagnosis of zinc deficiency and excess in individuals and populations

Brittmarie Sandström

Abstract

Efficient regulation of zinc homeostasis makes the diagnosis of zinc deficiency and excess difficult, and no single measurement is sufficiently specific or sensitive on its own for this purpose. Dietary zinc content and availability, the prevalence of stunting, and average plasma zinc concentrations in a population could give an estimate of the risk of zinc deficiency. In individuals, plasma zinc concentration, urinary zinc excretion, and the response to an increased zinc intake can provide information about the metabolic state with regard to zinc. Zinc has a low toxicity, but an excessive intake could interfere with copper metabolism.

Introduction

Several characteristics of zinc metabolism have to be kept in mind when the risk or presence of deficiency or excess of zinc is to be assessed in individuals and populations. There is no storage of zinc in the conventional sense. The majority (80%–90%) of zinc in the body is found in muscle and bone. However, the concentration of zinc in muscle and most other cells is kept constant over long periods of low intake and is not substantially decreased, even in conditions of clinical zinc deficiency. In conditions of catabolism, zinc is released from muscle and may be available for biological functions. In a similar way, bone resorption will lead to release of zinc, but there is no known mechanism for mobilizing zinc from bone or tissues to cover an increased requirement of zinc. The constant tissue and body zinc content is achieved by changes in absorptive efficiency and endogenous excretion of zinc. The changes in intestinal endogenous excretion are quantitatively the most important, and apparent zinc balance can thus be maintained over a wide range of intakes.

The clinical features of severe zinc deficiency are growth retardation, delayed sexual and bone maturation, dermatitis, loss of hair, diarrhea, defects in the immune system, impairment of taste acuity, and behavioral changes [1]. Supplying zinc rapidly reverses the external signs of deficiency and improves the other characteristics. However, none of these signs of zinc deficiency is sufficiently specific or sensitive on its own to detect marginal or subclinical zinc deficiency. In analogy with approaches made for other nutrients, attempts have been made to evaluate zinc status from measurements of zinc concentration in different tissues, the activity of zinc-dependent enzymes, body pool sizes, and selected functional indices. Each of these measurements has advantages and limitations, and their usefulness depends on the context in which they are to be applied. Some relevant aspects of these indices are summarized below. Information about these measurements can be found elsewhere [2, 3]. Their usefulness is also evaluated from results of experimental zinc deprivation in humans and response to supplementation in population studies.

Putative indices of zinc status

Compositional analyses

Serum or plasma zinc

The most commonly used measurement of zinc status is plasma or serum zinc, despite the fact that less than 0.1% of body zinc is present in plasma and the concentration appears to be under strict homeostatic control. Zinc can be temporarily redistributed from plasma to other tissue or the concentrations can be changed by conditions unrelated to zinc status. Infections, fever, food intake, and pregnancy lower plasma zinc, whereas starvation and catabolism increase it.

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Plasma zinc is also depressed at times of rapid tissue growth [4]. Despite these limitations, the fact that plasma zinc concentrations are normally distributed in healthy populations makes it possible to establish reference values to be used to identify individuals at risk for a low zinc status. An average population plasma zinc concentration lower than that of a well-nourished population should consequently be regarded as an indication of a greater risk of zinc deficiency. In zinc supplementation studies in children, initial average plasma zinc concentrations less than 12.2 µmol/L appeared to be associated with a higher body response in weight gain [5].

When collecting plasma samples for zinc analysis, precautions have to be taken to avoid hemolysis and contamination of samples and reagents with rubber and other potential sources of zinc. Reference serum samples are available and should be used for quality control. A fasting plasma zinc concentration of 9 mmol/L or a postprandial concentration of 8.4 mmol/L has been suggested as a cutoff levels for low plasma zinc concentration.

Erythrocyte zinc

The concentration of zinc in erythrocytes is approximately 10 times higher than that in plasma. The slow turnover rate of erythrocytes means that their content of zinc cannot reflect recent changes in zinc supply, but they may be useful for studies of chronic zinc deprivation. Experimental zinc depletion studies lasting up to 10 to 12 weeks have, however, not shown consistent changes in erythrocyte zinc. Cutoff levels have not been established, and at present erythrocyte zinc is not a useful measure of zinc status.

Leukocyte zinc

Because of their shorter half-life, leukocytes are assumed to be more sensitive to changes in zinc supply than erythrocytes. However, the different subsets of white cells have different half-lives and also different zinc contents. Thus, analyses of zinc content of mixed leukocytes may be difficult to interpret. The differential separation of leukocyte subsets is also technically difficult.

Hair zinc

Integumental and hair zinc concentrations respond to changes in zinc supply, and monitoring of hair zinc content appears to be a useful marker for the response to an increased zinc supply [6]. However, with severe zinc deprivation, increased hair zinc levels have been observed in animals and malnourished children [7], probably because of a reduced rate of hair growth. The sampling technique (e.g., the distance from the scalp) and the cleaning of the samples, with removal of external contamination without extracting intrinsic zinc, are also crucial for interpretation of the zinc content of hair [8]. A cutoff level of 1.07 µmol/g has been suggested as an indication of low zinc status.

Urinary zinc excretion

At adequate zinc intakes, 24-hour urinary zinc excretion is relatively constant (approximately 4 to 9 mmol per 24 hours) and does not reflect day-to-day variations in zinc intake. At chronically low zinc intakes, urinary zinc excretion is reduced, apparently as part of the homeostatic regulation of body zinc content. Muscle catabolism increases urinary zinc excretion, and anabolism may depress it. Drugs with chelating abilities can increase urinary zinc excretion, as can alcoholism and liver disease. Thus, the pathological and metabolic state of the individual should be considered when evaluating urinary zinc excretion, and this measure does not stand alone as a useful indicator of zinc deprivation in an individual. Similar to hair zinc, determination of baseline and postintervention urinary zinc excretion and comparison with normal values may be useful for evaluating the efficiency of zinc intervention programs.

Rapidly exchangeable zinc pools

The rapid onset and disappearance of clinical zinc-deficiency symptoms suggest the presence of an easily accessible pool of zinc. Isotope studies evaluating turnover rate in plasma or urinary samples have revealed a relactively small, rapidly exchangeable pool of zinc on the order of 100 to 200 mg (approximately 10%–20% of total body zinc) [9–12]. The technique requires advanced analytical equipment and technical expertise, which, together with the high cost of stable isotopes, limits its usefulness for population studies. With further evaluation of this technique in chronic or acute zinc depletion and repletion, it may be used as a gold standard for establishing functional cutoff levels for more easily measured indices, e.g., plasma zinc.

Functional indices

In theory, the activities of zinc-dependent enzymes in plasma or blood cells should be useful as functional indices of zinc status. A number of enzymes have been studied in this respect, e.g., alkaline phosphatase, carboxypeptidase, lactate dehydrogenase, 5′-nucleotidase, thymidine kinase, D-amino–laevulinic acid dehydratase, and angiotensin-1–converting enzyme. However, so far none of them has proven to be a reliable indicator of zinc deprivation.

On the basis of observations in severe zinc deficiency, other functional tests have been suggested as indices of zinc status, e.g., taste acuity, dark adaptation ability (electroretinography), cutaneous hypersensitivity, and leukocyte chemotaxis. Although these tests have not been found to be specific enough to diagnose zinc deficiency in a population or an individual, they can be useful in monitoring the response to zinc supplementation or other improvements of zinc supply.

Experimental zinc deprivation and indices of zinc status

A limited number of experimental zinc-deprivation studies have been conducted in healthy, presumably well-nourished adult subjects over periods ranging from four to nine weeks up to six months. In extreme zinc-depletion studies using semipurified formula diets and intakes close to zero for five to nine weeks [13–15], marked reductions in plasma zinc and urinary and fecal zinc excretion were observed in all subjects. The decline in urinary zinc paralleled the changes in plasma zinc for an individual, but the relation differed among subjects. Some individuals showed minor clinical signs, such as dermatitis and sore throat, which could be attributed to zinc deficiency, whereas more obvious zinc deficiency signs (acneiform skin lesions) were observed in only one case [15]. The rapid response to these low zinc intakes suggests that accessible zinc stores are relatively small.

The responses to acute and complete withdrawal of zinc supply, however, may not fully reflect the response to more realistic dietary zinc deprivations. When the zinc intake of presumably well-nourished adults was reduced from 250 µmol/day (a typical zinc intake in American adults) to 84 µmol/day (around the minimum intake in most dietary intake studies), no changes in urinary or plasma zinc were observed, and the body zinc content seemed to be maintained mainly by decreased endogenous fecal zinc excretion [16]. Also, with lower zinc intakes (40–50 µmol/day), circulating zinc concentrations and activities of zinc-containing enzymes can be maintained within normal range over several months [17, 18]. Johnson et al. [19] studied the effect of five levels of zinc intake, from 159 to 22 µmol/day in 35-day periods. Only at the lowest intake was plasma zinc reduced from 12.7 ± 1.2 to 11.2 ± 2.8 mmol/L. The probable explanation for the modest response to low zinc intake is a high bioavailability of zinc from the semisynthetic diets, allowing for maximal adaptation in absorption and endogenous excretion.

These adaptive mechanisms may not be as efficient when diets with a low availability of zinc are consumed. Dietary manipulation to achieve a low zinc content and a low bioavailability has been used in experimental studies to induce mild zinc deficiency in adults. Rabbani et al. [20] used an EDTA-washed soy-based diet, and Ruz et al. [21] used a diet with soy protein and albumin with added sodium phytate. In 15 male subjects (mean age, 25 years), intake of a diet low in zinc (61 µmol/day) and high in phytate (1.32 g/day; phytate:zinc molar ratio, 58) for six weeks resulted in a decline in plasma zinc from 14.8 ± 1.7 to 12.2 ± 2.0 µmol/L and a decline in urinary zinc from 8.0 ± 2.7 to 4.3 ± 2.3 µmol/L [21]. Changes in taste acuity and cellular immune response were also observed, whereas cellular zinc concentrations were not affected. In another study [22], a significant decline in alkaline phosphatase activity in erythrocyte membranes was observed. In eight young adult men of the same age as those in the study by Ruz et al. [21], intake of 63.1 µmol zinc/day for six months reduced plasma zinc from 17.6 ± 0.5 to 16.1 ± 1.8 µmol/L [23]. Mean urinary zinc output was reduced from 11.1 ± 2.8 to 7.7 ± 2.0 µmol/24 h. Cellular zinc levels declined significantly only after 20 weeks, whereas a reduction in lymphocyte ecto-5′-nucleotidase activity was observed after four to eight weeks of zinc restriction [24]. The endogenous fecal zinc excretion was reduced from 65.2 µmol/day at baseline to 47.7 µmol/day after two months and 27.1 µmol/day at the end of the six months of depletion. Zinc absorption was significantly increased at two and four months of zinc restriction but was not significantly different from baseline at the end of the depletion period. This suggests that the endogenous fecal excretion is crucial for zinc homeostasis. Any impairment of this function, e.g., by chronic or acute intestinal infection and diarrhea, would increase the risk of zinc deficiency at marginal to low intakes of zinc.

The results from the experimental zinc-depletion studies suggest that a reduction in urinary zinc excretion is an early marker for a low body zinc supply. Urinary zinc excretion drops before any detectable changes in serum or plasma zinc. The changes in plasma and urinary zinc observed in the different experimental studies are, however, not consistent, and the values are often within normal ranges, even after long-term marginal zinc intakes. Most of the other suggested indices of zinc status are not affected, even in studies with zinc intakes lower than the minimum intakes of most populations.

Assessment of zinc status in individuals and populations

The approaches taken for assessment of zinc status depend on the purpose of the assessment. Different techniques might be applied, depending on whether the purpose is to assess the risk of deficiency, the actual prevalence of deficiency, or the response to an intervention program aimed at improving the zinc supply. An evaluation of the dietary zinc supply, not only in regard to total zinc intake but also with an estimate of the amount of absorbable zinc, will give an initial indication of the risk of zinc deficiency in a population. According to available data for zinc requirement and food intake in different countries, 68% to 94% of children in a number of developing countries were considered at risk for zinc deficiency, as compared with only 1% of Canadian children [25]. For assessing the prevalence of zinc deficiency in a population, a careful evaluation of plasma zinc concentrations in representative samples of the population and of the prevalence of stunting seems to be useful. The prevalence of conditions that increase the requirement of zinc, e.g., diarrhea, infections, and malnutrition, also needs to be considered. Additional information can be obtained from measurements of hair zinc concentration and urinary zinc excretion.

To monitor the response to zinc intervention in a population, representative sampling of plasma zinc is still the best available marker of zinc status. Whenever possible, functional indices, such as immune response and dark adaptation ability, should be included.

In individuals, a serum or plasma zinc value below reference values for the population, in the absence of acute infections, and a low urinary zinc excretion suggest a marginal zinc status. Enzyme assays or molecular tools may be used in the future as they become available. Zinc has a central role in regulation of gene expression, especially through the metal response elements of metallothionein genes, and it was recently demonstrated that metallothionein mRNA in lymphocytes responded to a change in zinc intake from 210 to 70 µmol/day, while plasma zinc was unaffected [26].

Zinc toxicity and assessment of excess zinc

Zinc has a low toxicity. Acute toxicity symptoms, such as nausea, vomiting, diarrhea, fever, and lethargy, are observed only after ingestion of gram doses. When zinc intake is increased, homeostasis is maintained through increased urinary and endogenous fecal excretion. Long-term zinc intakes higher than requirement could, however, interact with the metabolism of other trace elements. Interactions with copper are well described. At an intake of 50 mg/day, changes in CuZn-superoxide dismutase in erythrocytes have been reported [27, 28]. At higher doses of zinc (450–660 mg/day), impairments of indices of copper status and anemia and changes in serum lipid patterns and immune response have been observed [29–32]. Nutritional rehabilitation of marasmic children with a zinc-fortified milk appears to impair monocyte function [33]. Dose-response studies of the effect of increased zinc intake on copper status and immune response are lacking. The above-cited studies suggest, however, that care should be taken not to impair copper status during zinc intervention studies.

Research needs

Despite the limitations of serum zinc as an indicator of zinc status, it remains the only option in many situations. The relation between serum zinc concentration, the rapidly exchangeable zinc pool size, and functional or other signs of zinc deficiency needs to be established. If a critical zinc pool size associated with impairment of zinc-dependent functions can be identified, it may also be possible to establish functional cutoff levels of serum zinc for individuals and for average population values associated with an increased risk of deficiency. Identification of early markers of adaptive changes in zinc metabolism would also be useful to identify individuals or population groups at increased risk of zinc deficiency. Before large population interventions are undertaken to improve the availability and consumption of zinc in populations, the lowest dose of zinc with no measurable negative effects on copper or immune status needs to be established.

References

1. Hambidge KM. Zinc. In: Mertz OW, ed. Trace elements in human and animal nutrition. Orlando, Fla, USA: Academic Press, 1986:1–137.
2. Solomons NW. On the assessment of zinc and copper nutrition in man. Am J Clin Nutr 1979;32:856–71.
3. Aggett PJ, Favier A. Zinc. Int J Vitam Nutr Res 1993;63:247–316.
4. Golden BE, Golden MHN. Plasma zinc, rate of weight gain, and the energy cost of tissue deposition in children recovering from severe malnutrition on a cow's milk or soya protein based diet. Am J Clin Nutr 1981;34:892–9.
5. Brown KH, Peerson JM, Allen LH. Effect of zinc supplementation on children's growth: a meta-analysis of intervention trials. Bibl Nutr Dieta 1998;54:76–83.
6. Gibson RS, Vanderkooy PDS, MacDonald AC, Goldman A, Ryan BA, Berry M. A growth-limiting, mild zinc-deficiency syndrome in some southern Ontario boys with low height percentiles. Am J Clin Nutr 1989;49:1266–73.
7. Erten J, Arcasoy A, Cavdar AO, Cin S. Hair zinc levels in healthy and malnourished children. Am J Clin Nutr 1978;31:1172–4.
8. Hambidge KM. Hair analyses: worthless for vitamins, limited for minerals. Am J Clin Nutr 1982;36:943–9.
9. Wastney ME, Gökmen IG, Aamodt RL, Rumble WF, Gordon GE, Henkin RI. Kinetic analysis of zinc metabolism in humans after simultaneous administration of ^{65}Zn and ^{70}Zn. Am J Physiol 1991;260:R134–41.
10. Fairweather-Tait SJ, Jackson MJ, Fox TE, Wharf SG,

Eagles J, Croghan PC. The measurement of exchangeable pools of zinc using the stable isotope ^{70}Zn. Br J Nutr 1993;70:221–34.
11. Miller LV, Hambidge KM, Naake VL, Hong Z, Westcott JL, Fennessey PV. Size of the zinc pools that exchange rapidly with plasma zinc in humans: alternative techniques for measuring and relation to dietary zinc intake. J Nutr 1994;124:268–76.
12. Sian L, Mingyan X, Mille LV, Tong L, Krebs NF, Hambidge KM. Zinc absorption and intestinal losses of endogenous zinc in young Chinese women with marginal zinc intakes. Am J Clin Nutr 1996;63:348–53.
13. Hess FM, King JC, Margen S. Zinc excretion in young women on low zinc intakes and oral contraceptive agents. J Nutr 1977;107:1610–20.
14. Baer MT, King JC. Tissue zinc levels and zinc excretion during experimental zinc depletion in young men. Am J Clin Nutr 1984;39:556–70.
15. Taylor CM, Bacon JR, Aggett PJ, Bremner I. Homeostatic regulation of zinc absorption and endogenous losses in zinc-deprived men. Am J Clin Nutr 1991;53:755–63.
16. Wada L, Turnlund JR, King JC. Zinc utilization in young men fed adequate and low zinc intakes. J Nutr 1985;115:1345–54.
17. Lukaski HC, Bolonchuk WW, Klevay LM, Milne DB, Sandstead HH. Changes in plasma zinc content after exercise in men fed a low-zinc diet. Am J Physiol 1984; 247:E88–93.
18. Milne DB, Canfield WK, Gallagher SK, Hunt JR, Klevay LM. Ethanol metabolism in postmenopausal women fed a diet marginal in zinc. Am J Clin Nutr 1987;46:688–93.
19. Johnson PE, Hunt CD, Milne DB, Mullen LK. Homeostatic control of zinc metabolism in men: zinc excretion and balance in men fed diets low in zinc. Am J Clin Nutr 1991;57:557–65.
20. Rabbani PI, Prasad AS, Tsai R, Harland BF, Fox MRS. Dietary model for production of experimental zinc deficiency in man. Am J Clin Nutr 1987;45:1514–25.
21. Ruz M, Cavan KR, Bettger WJ, Thompson L, Berry M, Gibson RS. Development of a dietary model for the study of mild zinc deficiency in humans and evaluation of some biochemical and functional indices of zinc status. Am J Clin Nutr 1991;53:1295–1303.
22. Ruz M, Cavan KR, Bettger WJ, Gibson RS. Erythrocytes, erythrocyte membranes, neutrophils and platelets as biopsy materials for the assessment of zinc status in humans. Br J Nutr 1992;68:515–27.
23. Lee D-Y, Prasad AS, Hydrick-Adair C, Brewer G, Johnson PE. Homeostasis of zinc in marginal human zinc deficiency: role of absorption and endogenous excretion of zinc. J Lab Clin Med 1993;122:549–56.
24. Meftah S, Prasad AS, Lee D-Y, Brewer G. Ecto 5 nucleotidase (5’NT) as a sensitive indicator of human zinc deficiency. J Lab Clin Med 1991;118:309–16.
25. Gibson RS, Ferguson EL. Assessment of dietary zinc in a population. Am J Clin Nutr 1998;68:430–4.
26. Allan AK, Hawksworth GM, Woodhouse LR, Sutherland B, King JC, Beattie JH. Lymphocyte metallothionein mRNA responds to marginal zinc intake in human volunteers. Br J Nutr 2000;84:747–56.
27. Fischer PWF, Giroux A, L’Abbé MR. Effect of zinc supplementation on copper status in adult man. Am J Clin Nutr 1984;40:743–6.
28. Yadrick MK, Kenney MA, Winterfeldt EA. Iron, copper, and zinc status: response to supplementation with zinc or zinc and iron in adult females. Am J Clin Nutr 1989;49:145–50.
29. Porter KG, McMaster D, Elmes ME, Love AHG. Anaemia and low serum-copper during zinc therapy. Lancet 1977;ii:774.
30. Hooper PL, Visconti L, Garry PJ, Johnson GE. Zinc lowers high-density lipoprotein-cholesterol levels. JAMA 1980;244:1960–1.
31. Chandra RK. Excessive intake of zinc impairs immune responses. JAMA 1984;252:1443–6.
32. Patterson WP, Winkelmann M, Perry MC. Zinc-induced copper deficiency: megamineral sideroblastic anemia. Ann Intern Med 1985;103:385–6.
33. Schlesinger L, Arevalo M, Arredondo S, Lönnerdal B, Stekel A. Zinc supplementation impairs monocyte function. Acta Paediatr 1993;82:734–8.

Dietary sources of zinc and factors affecting its bioavailability

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Abstract

Zinc is one of the more ubiquitous of nutrients, being found in modest amounts in a large number of foods. Human evolution has undoubtedly shaped the needs for zinc to be absorbed from our beverages and foods of both animal and plant origin in the diet. Different environmental and ecological circumstances modify the amount of zinc that needs to become available to individuals of different regions. We use an acronym approach to review and understand the bioavailability of zinc. The biological availability of zinc can be limited by many factors intrinsic and extrinsic to the host, and it can be enhanced by few. Challenges remain in assessing the bioavailability of zinc compounds as fortificants and in developing strategies to improve the uptake of the metal by reducing phytate and tannin content of diets, either through food technology or plant genetics.

Background

Zinc and human evolution

Some 99% of the evolution of *Homo sapiens* occurred in the hunter-gatherer condition [1]. Humans are clearly omnivorous, but how well the wide variety of edible species of flora and fauna consumed in prehistory provided evolving humans with zinc is not known. Recent estimates of the proportion of foods of animal and plant origin during this long period of hominid evolution have been revised [2]. It is now asserted that our hunter ancestors obtained anywhere from 65% to 75% of their calories from animal sources, and that their lifestyle obligated a prodigious daily intake of energy to keep up with the hunt. Accepting the premises of Eaton and Konner [1] that the genetic imprinting for contemporary humans occurred during the Paleolithic period, the metabolic adaptation for humans' nutrient needs reflects what they received and utilized as hunter-gatherers over some 260,000 or more years of cultural evolution.

It is a safe conjecture that the emergence into the ages of pastoralist and agriculturalist, some 40,000 [3] and 10,000 [4] years ago, respectively, produced a situation in which the newly dominant foodstuffs in the diet, milk and cheese for pastoralists and cereals and tubers for agrarians, were poor sources of available zinc. At no time during the last 400 generations, i.e., through the agricultural era, has either the intake of zinc or its bioavailability been as high as it was for the 10,000 generations that preceded it.

Inadequacy of human zinc nutriture

Pioneering studies in the early 1960s in Iran [5, 6] and Egypt [7] described endemic, zinc-responsive dwarfism syndromes. Nevertheless, it has taken almost four decades to advance to a discussion of the policy and programmatic issues of zinc deficiency. This delay probably has two primary reasons. First, in the 1960s the public health nutrition community was concerned with protein-energy malnutrition, and micronutrients received little academic attention or financial support. It was only with the shift to issues of "hidden hunger" (micronutrient malnutrition) that an interest developed in zinc. Second, only proven limitation of social and economic development [8] or excess morbidity and mortality [9] related to nutrient deficiencies motivates policymakers to action. It was only in the late 1990s that adverse effects of zinc deficiency in some populations began to emerge, resulting in serious interest in dietary sources of zinc and its bioavailability.

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Alternative strategies for improving nutrient status with respect to zinc

To the extent that the micronutrient status of a population is insufficient, options for positive change must be considered. A generic battery of four basic strategies can be identified for improving nutrient status: supplementation, fortification, diversification of the diet, and other health measures to avoid losses [10]. These can be applied singly or in various combinations.

Supplementation is a medical type of intervention, with little relation to food or diet. Fortification and diversification of the diet, however, both have to do with selection of foods, and it is useful to consider them together. Moreover, illnesses can interfere not only with the retention of nutrients, but also with obtaining and consuming food sources of nutrients. The efficacy or effectiveness of these strategies should be evaluated for biological impact. Most considerations of zinc interventions beg the question of assessing zinc status. Unfortunately, no reliable indices of zinc status suitable to field surveys or clinical management are yet available [11, 12]

Enhancing nutrient bioavailability

Another potential strategy is the modification of the diet or specific foods so that their nutrients become more bioavailable. Zinc is a candidate for this approach [13]. However, the margin between safe and excessive intakes of zinc is narrow [14]. The recommended adult dietary allowance for zinc in the United States is 15 mg per day for men and 12 mg per day for women [15]. On the basis of studies with medicinal zinc, the suggested upper limit for daily zinc exposure is 21 mg [14], but this does not take absorption in diets into account.

Zinc bioavailability from the human diet

Analysis of zinc bioavailability factors

Professor Clive West, of the Wageningen Agricultural University, has developed the acronym, SLAMENGHI [16], to guide analysis of nutrient bioavailability. Table 1 lists the factors represented by this acronym.

Species

Zinc is a transition element in the periodic table of elements, with atomic number 30 and atomic weight 65.37, as a consequence of its mixture of five stable isotopes: ^{64}Zn, ^{66}Zn, ^{67}Zn, ^{68}Zn and ^{70}Zn. It has two radioisotopes useful in human and animal research, ^{65}Zn and ^{69}Zn. Zinc is stable in its divalent cationic state, Zn (II), and is neither a reducing nor an oxidizing agent [17]. It forms inorganic salts and organic complexes with acids and other negatively charged compounds. The unique stability of its valence, its versatile coordination chemistry, and its ionic radius have been credited by Chesters [17] for its roles in the biological world.

Molecular linkages

Because of its chemical nature, zinc does not form covalent linkages in molecules. Its chemistry is based on electronic coordination. However, there is wide diversity in the solubility of the various compounds proposed as potential fortificants for zinc. The biological availability of zinc to animals and humans in over a dozen compounds has been investigated: inorganic salts (zinc chloride, zinc sulfate, zinc oxide, zinc carbonate, zinc ammoniate), organic acids (zinc acetate, zinc citrate, zinc gluconate, zinc lactate, zinc stearate, zinc picolinate, zinc ascorbate), and amino acids (zinc-histidine complex, zinc-methionine complex, zinc-lysine-complex) [18, 19]. The standard has generally been zinc sulfate.

Davidsson [19] recently summarized the characteristics of color, taste, odor, aqueous solubility, and solubility in other solvents for three inorganic salts and five zinc-acid complexes of potential use in food fortification. She showed that the oxide, stearate, lactate, and citrate are all of very low solubility. That is, at neutral pH they remain tightly complexed in water and most beverages. A soluble salt is the most bioavailable, and an insoluble complex is the least.

Amount of zinc consumed in a meal

The fractional absorption of zinc (the percentage of an orally administered dose absorbed) responds to the total amount of zinc delivered. The more zinc in a meal (or in an isolated oral dose), the less is the fractional absorption of the zinc [20, 21]. This is an almost universal behavior in intestinal absorption [22]. Hence, when more zinc is consumed, there is a diminishing return in the efficiency of uptake of zinc, although the net absorption continues to increase as a function of the dose.

TABLE 1. SLAMENGHI factors for bioavailability

Species of the metal
Linkages, molecular
Amount of zinc consumed in a meal
Matrix into which zinc is incorporated
Effectors of absorption
Nutrient (zinc) status of the host
Genetic factors
Host-related factors
Interactions, mathematical

Source: ref. 16.

Matrix into which zinc is incorporated

The zinc in foods and, to some extent, the zinc in beverages such as milk, yogurt, or blood libations is found either in its functional form in the zinc metalloenzymes or in intracellular storage forms, associated with metallothionein.

In theory, since pepsin and pancreatic enzymes are efficient in releasing the amino acids as small peptides and free amino acids into the intestinal lumen, the protein-associated zinc in foods should be liberated during normal digestion. We found that the decrease in plasma uptake of zinc from a combination of Atlantic oysters and maize tortillas was proportionately less than when an equal amount of zinc was supplied by tortillas and zinc sulfate [23]. We also developed plasma zinc-response curves for cooked beef [24]. There are indications that matrix factors may be at work, at least in protecting the zinc from absorptive inhibitors. Finally, the zinc already complexed with phytate in vivo in plants may have relatively lower bioavailability than free zinc coming into the presence of phytic acid in the intestine.

Effectors of absorption

Inhibitors

Naturally occurring and synthetic constituents of the human diet can interfere with the absorption, utilization, or both of dietary zinc. Two general mechanisms for the inhibition of absorption of the cation are chelation precipitation and competitive inhibition. A food constituent could, at least in theory, disrupt the uptake of the metal by deactivating energy-dependent intestinal uptake mechanisms.

It has been observed that some foods and diets are associated with poor intestinal zinc absorption, including diets based on soy and on whole-grain cereals. In fact, the list of foods that reduce the uptake of zinc, as compared with the uptake of zinc administered in an aqueous solution, represents almost every food and meal that has been examined. To give examples only from human experiments, these foods include hamburger on a bun, celery, lemon, coffee, milk, egg, tortilla, black beans, whole-grain cereal breads, Iranian flat breads, and varieties of soy-based foods [25]. Only bacon failed to reduce the relative uptake of zinc [26].

A number of chemically defined constituents of plants have been identified as inhibitor candidates and studied in either human subjects or laboratory and farm animals. These include specific dietary fiber components [27, 28] and tannins (polyphenols) [29]. Phytic acid is an inhibitor of zinc absorption in most animal and human studies [30, 31]. Two studies illustrate this effect with a soy-based food fed to young children [32, 33]. The presumptive mechanism of interference with absorption is intraluminal binding of zinc in insoluble complexes.

Similarly, Mallaird-reaction products produced in the cooking of tortillas influenced zinc uptake negatively [34]. Although ethylenediamine tetraacetic acid (EDTA) improved zinc absorption in an animal model with soy protein as the source [30, 35], it acted either as an inhibitor [23] or as an enhancer [36] in humans when presented as sodium-iron–EDTA. Each of the aforementioned inhibitors is presumed to exert its effect by complexing or binding with zinc.

The agents that probably work in a competitively inhibitory manner are other cations. Both copper and iron can compete with zinc at common intestinal binding sites, but only iron is commonly consumed in a multiple excess over zinc. This can occur in isolated nutrient supplements [37] and in iron-fortified foods. In natural foods that are sources of both iron and zinc, the molar ratio is generally close to 1:1 and rarely varies to 1:2 or 2:1. By contrast, in human experiments the inhibitory effect is generally seen at iron/zinc ratios above 3:1 and with more than 25 mg of total iron consumption, presumably as a result of a direct competitive interaction. Heme iron is not an inhibitor.

In an isolated, perfused intestinal rat model, zinc chelated to casein phosphopeptides of 1–25 β-casein was compared with zinc sulfate in its interaction with iron, at Fe/Zn ratios of 1:2, 5:1, and 10:1 in the form of ferrous gluconate or an iron complex of the phosphopeptide [38]. Dramatic reduction in zinc absorption was seen when the sulfate salt was combined with iron gluconate in the iron-excess ratios, but when zinc was present as the casein peptide complex, neither form of iron reduced zinc uptake to any appreciable extent. Most of the studies reviewed, including our own, used simple designs without complex feedings or meals. As with iron, once a meal setting or diet designs are introduced, the clarity of interactions is blurred [39, 40]. With isolated zinc supplements, decreased absorption efficiency is seen in the presence of two- to threefold excesses of elemental iron.

The question of an important calcium-inhibitory interaction has long been unresolved. Calcium is an omnipresent component of milk, infant formula, and other foods. Dairy and nondairy calcium may have different effects [41].

Coadaptation is a concept [22] based on the original Hill and Matrone [42] theory of biological interaction of chemically similar metals. The absorption of a metal by the intestines is affected by a deficiency or excess of another chemically similar metal. Pollack et al. [43] observed that iron-deficient animals had an increase in a series of nonferrous transition elements. In humans, however, iron deficiency does not increase zinc absorption.

Hambidge et al. [44] illustrated an inverse relationship between the cumulative dosage of iron consumed as a prenatal supplement and circulating zinc concentrations in pregnant women, a finding confirmed in iron-deficient university women in California [45]. Recently, impairment of the zinc status of infants fed a mixture of breastmilk and infant formula was observed when the complementary formula was iron-fortified [46].

Enhancers

In theory, enhancers of zinc uptake could work at the level of the enterocytes or in the lumen of the intestine, either by releasing zinc from inhibitory substances or by directly assisting in the transport of the metal across the intestinal membrane. However, red Zinfandel wine is the only food or beverage that has been shown to enhance zinc absorption [47]. In the 1970s and early 1980s, there was a search for a "zinc-binding ligand" in pancreatic secretions and in breastmilk, but none was found [25, 31, 48, 49].

Vitamin C was also investigated and found not to be an enhancer of zinc absorption. Gibson and Ferguson [18], in their review article, mention a number of small organic compounds (methionine, cysteine, cysteine-containing peptides, citric acid, and lactic acid) that are advanced as potential enhancers of zinc absorption. However, it is hard to conceive of a meal or dietary situation in which substantial concentrations of these compounds would accumulate in the upper intestinal lumen.

Nutrient (zinc) status of the host

Much research has been done to establish whether and how the zinc status of an organism is regulated. Evidence for homeostatic regulation, with conservation in states of zinc scarcity and less retention in states of adequacy and excess, has been reported in rats [50].

The nutritional needs of the host influence absorption. In pregnancy, up-regulation of zinc absorption appears to be a mechanism of adaptation to provide the fetus, products of conception, and maternal tissues with increased zinc to support the pregnancy. Fung et al. [51] showed a distinct trend to greater fractional absorption through the trimesters of pregnancy, a finding somewhat confounded by an unintended spontaneous increase of 3 mg in daily zinc intake.

Genetic factors

Potential excessive zinc absorption and a confirmed zinc malabsorption based on genetic constitution have been reported. Idiosyncratic hyperabsorption of zinc, analogous to hemochromatosis or African hemosiderosis with iron or Wilson's disease for copper, and zinc hypoabsorption conditions, analogous to Menkes' syndrome for copper, have been a curiosity in clinical medicine. Smith et al. [52] described a familial hyperzincemia in which the members of this lineage had circulating zinc concentrations in excess of 300 μg/dl. The error was ascribed to abnormal circulating binding affinity, rather than to excessive uptake.

Acrodermatitis enteropathica is a progressive, fatal dermatological disease characterized by skin rashes, hair loss, immune deficiencies, persistent diarrhea, and malabsorption. Once it was recognized that supplementary zinc would alleviate the signs and symptoms [53], the nature of the disorder became clear. Acrodermatitis enteropathica represents a reduced intestinal zinc-absorption efficiency, which can be compensated for by high intakes of oral bioavailable zinc. The genes controlling these conditions have not been identified.

Host-related factors

Intestinal diseases, such as celiac disease, Crohn's disease, protein-energy malnutrition, and intestinal parasitoses, that produce malabsorptive states affect the uptake of dietary zinc [54]. Protozoal infection of the intestine may be an important impediment to efficient zinc uptake [55]. Acute diarrhea is associated with net loss of zinc from the intestine [56].

Pancreatic insufficiency is a factor in zinc absorption, since ligating the pancreatic duct interferes with zinc absorption. A decrease in food zinc uptake has been demonstrated in cystic fibrosis patients, which was reversed with the addition of supplemental digestive enzymes [57]. This is attributed to the requirement to release zinc from its protein matrices in tissues of plant and animal origin.

Gastric acidity is a modifier of nutrient absorption. *Helicobacter pylori* infection can cause hypochlorhydria, and antacids and acid-blocking drugs are widely used to control the symptoms of peptic disease due to this organism. The net consequence is that many meals enter stomachs with low gastric acidity. Because acidity is important in solubilizing salts, hypochlorhydria would be expected to reduce zinc availability. Sturniolo et al. [58] present evidence in favor, and Serfaty-Lacrosniere et al. [59] present evidence against, an important effect of low gastric acidity on the efficiency of zinc uptake. Given that liberation of zinc from its protein matrix is a factor, the loss of pepsin activity from *H. pylori* infection is a consideration beyond that of its effect on the intraluminal pH.

Systemic infections and fever may cause a transient increase in zinc absorption. Pekarek and Evans [60] found more avid uptake of zinc in experimental rodents treated with leukocyte endogenous mediators, a preparation rich in what we now recognize as inflammatory cytokines. However, since acute and chronic inflammatory diseases are most often associated with a negative effect on appetite, any increased efficiency in uptake of zinc is probably offset by a diminished total intake of the metal.

Generalizations about the bioavailability of zinc from human dietaries

The net result of these considerations is that the biological availability of zinc can be limiting. As early as 1976, the World Health Organization (WHO) estimated that diets could be classified as having high (40%), medium (20%), and low (10%) biological availability [61]. A subsequent study [62] used a similar assumption in deriving "population mean intakes for dietary zinc" for "high-availability," "medium-availability," and "low-availability." However, assigning a bioavailability classification to a cuisine is more of an art than a science. For zinc, we do not have the nomogram approach that Monsen et al. [63] brought to inorganic iron. With the absence of specific enhancers, the net biological availability of zinc from a diet or a meal would depend on the level of inhibitors.

There is a general consensus that the phytate/zinc molar ratio and the phytate calcium/zinc molar ratio times energy can usefully serve as predictors of the bioavailability of zinc [18, 64]. A critical cutoff for the phytate/zinc molar ratio of greater than 15 [65] or greater than 20 [66] has been debated. For the more complex index, phytate calcium/zinc ratio per MJ, a level greater than 22 has been associated with impaired zinc nutriture [67, 68]. However, it may be more useful to consider them as continuous variables in the absence of firm data about thresholds. An independent inhibitory effect of calcium, analogous to that with iron [69, 70], might be involved. The potential factors influencing the availability of zinc in animal flesh remain to be resolved [23, 24, 41].

What is clearly evident is that predictions of adverse interactions from experiments using pure chemical inhibitors often do not apply to empirical studies with whole meals or diets. What is certain, however, is that the efficiency of zinc absorption from diets is low, and is lowest of all in the traditional plant-based diets of agrarian societies. Factors reducing the availability of zinc in a meal and the effect on zinc of the pancreatic secretory response to the meal would be additive [71].

Sources of zinc in human diets

Theoretical concepts and constructs

Table 2 is an attempt to classify various food groups in terms of their potential to serve or not to serve as sources of zinc in human diets [72] It does not allow for zinc excreted into the intestine and then absorbed. Zinc is like calcium, but unlike most other nutrients, in that it is absorbed in the intestine not only when it comes in with meals, but also when it is resecreted into the lumen during the pancreatic secretory response to meals [71]. This results in a unique vulnerability to rapid depletion by absorption inhibitors.

TABLE 2. 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, chocolate, soft drinks, alcoholic drinks, sugars, jams, preserves
Poor (1–5)	Fish, fruits, refined cereal products, pastries, biscuits, cakes, puddings, tubers, plantains, sausage, french fries
Rich (4–12)	Whole grains, pork, poultry, milk, low-fat cheese, yogurt, eggs, nuts
Very rich (12–882)	Lamb, leafy and root vegetables, crustaceans, beef kidney, liver, heart, mollusks

Source: ref 72.

Cumulative–frequency graphs of food-specific nutrients such a vitamin A, riboflavin, calcium, and zinc show most of the diet contributing little or nothing. For example, milk and dairy products are generally the leading sources of calcium and riboflavin in Western nations. About half of all foods make some contribution of zinc to the diet and as such can be considered as "zinc sources." This is illustrated by tables 3 and 4, derived from a tabulation of the zinc concentration of foods given in *Bowes & Church's Food Values of Portions Commonly Used* [73]. Table 4 shows the classes of foods and specific within-class items that are zinc sources (defined as having at least 1 mg of zinc in a 100g portion). Table 3 lists those that are not sources of zinc. Whole classes of edible items are outside of the category of zinc sources according to this criterion. These include beverages, tubers, fruits, vegetables, shortenings and oils, spreads, spices, sweeteners and syrups, and virtually all soups. It is difficult, however, to find meats, nuts, seeds, legumes, and whole-grain items that do not provide more than 1 mg of zinc per 100 g of edible serving. It should be recognized that depending on the food source and the total composition of the diet, the zinc will be of a markedly different biological availability across sources and populations, and that intake will be overestimated if availability is not taken into account.

In terms of satiety and control of eating, the weight and bulk of foods are important, but they are secondary to the energy content of the food. Table 4 also gives zinc density per food. In descending order, the 10

TABLE 3. Foods containing less than 1.0 mg of zinc per 100 g of edible portion

Beverages: municipal tap water, beers, wines, soft drinks, coffee, fruit juices, teas, coconut milk
Milk and dairy products: cow's milk, goat's milk, yogurt, cocoa, eggnog, cream, sour cream, cottage cheese, cream cheese, soft goat cheese, ice cream, sherbet, gelatin desserts, puddings
Fish: salmon patties, fish fillet sandwich, fried scallops, freshwater bass, sea bass, cod, tuna, caviar, haddock, halibut, mackerel
Breakfast cereals: cream of wheat, farina, oatmeal
Grains and grain products: white bread, cakes, cookies, doughnuts, brownies, pancakes, cream puffs, croissants, bagels, pasta, rice, matzo
Tubers: french fried potatoes, hash brown potatoes, baked potatoes, carrots, beets, turnips, yams, taro
Vegetables: alfalfa sprouts, asparagus, broccoli, green leafy vegetables, yellow corn, leeks, lettuce, mushrooms, peas, pumpkin, squash, cole slaw, onion rings
Fruits: apples, berries, grapes, citrus fruits, raisins, avocadoes, tomatoes
Soups: chunky beef soup, clam chowder, minestrone
Nuts: breadfruit seeds, beechnuts, chestnuts
Shortenings and oils: all classes
Spreads: all classes
Spices: all classes
Sweeteners and syrups: all classes
Sweets and miscellaneous: hard candies, fudge, jellybeans, taffy, toffees, popcorn, coffee mate, bean and cheese burritos

Source: ref. 73.

most zinc-dense items, based on milligrams per 1,000 kcal, are Atlantic oysters, steamed king crab, bear meat, ready-to-eat cereal, steamed lobster, crab cake, Carnation breakfast bar, all cuts of beef, cooked octopus, and all cuts of lamb. None of these are economically available to developing-country populations. Thus the concentrated sources of zinc that do exist are expensive and uncommon, perishable, or both. Almost all are unlikely to be available to the most zinc-deficient vulnerable sectors of the population. The food-composition data of Bowes & Church are limited by small samples and lack of global representativeness. The International Network of Food Data Systems (INFOODS) initiative of the Food and Agriculture Organization (FAO) and the United Nations University is compiling and updating multiple food-composition databases specific to the foods of distinct regions of the world. For the future, these more population-specific food-composition data that are freely available electronically from FAO will be a prerequisite to understanding the zinc intake of populations and for implementing and evaluating nutritional interventions.

Removing the seed coat elements of the whole grain through milling reduces the phytic acid and fiber that inhibit zinc uptake. As a result, the efficiency of absorption of zinc from the milled flour is higher, but the amount of zinc is substantially lower. Sandström et al. [21], using 65Zn, found that "Despite the lower percentage absorption of zinc from the wholemeal bread, the absolute amount absorbed was comparable to, or even higher than, that from the white bread." This confirmed a finding based on metabolic balance studies [74] that most seed-based foods have low zinc density (if milled) or poor bioavailability (if unrefined).

Zinc sources through the life span

After weaning, the family diet is the source of zinc, but infants have a special dietary source of zinc in human milk. Milk is a very dilute source of zinc, but the bioavailability of zinc in milk is high. The low concentration of zinc in milk would tend to increase its fractional absorption and is probably a major determinant of the high efficiency. Moreover, human milk has a relatively low content of calcium as compared with bovine milk [75], although we do not know the threshold for a calcium effect on zinc absorption.

There is a wide range to choose from in seeking a recommended intake of zinc for infants and toddlers. The US recommended dietary allowance [15] specifies 5 mg of zinc daily. Work from the University of Colorado [76, 77] challenged the applicability of this level. Based on their considerations, Brown et al. [78] derived a 2.8 mg daily recommendation. The WHO/International Atomic Energy Agency (IAEA) [62] document specified different safe daily intakes, depending upon whether one was consuming a high-availability, medium-availability, or low-availability diet. They defined exclusive breastfeeding as consumption of a high-availability zinc diet, on the assumption that 80% of the zinc is absorbed. Their minimum values for safe population mean intakes for exclusively breastfed infants are 1.3 mg/day from birth to three months, 0.7 mg/day from three to six months, and 0.8 mg/day from six months to a year.

Several generalizations can be made about the zinc content and bioavailability of zinc in human milk. The content is relatively low. Zinc concentration is a function of the stage of lactation [79], with a 40% reduction in zinc concentration in mature milk over time. In colostrum, concentrations of zinc can be as high as 8 to 9 mg/L, falling to the range of 3 mg/L by two weeks of lactation, when the milk becomes mature. Typical ranges of concentrations of zinc in mature milk range from 0.20 to 4.0 mg per 100 ml [80–90]. Brown et al. [78] have provided a detailed and comprehensive nomogram to predict the amount of energy from breastmilk that is consumed by exclusively

TABLE 4. Foods containing 1.0 mg or more of zinc per 100 g of edible portion

Food	Zn content of standard portion (mg)	Weight of standard portion (g)	Energy value of standard portion (kcal)	Zn content of edible portion	
				mg/100 g	mg/1000 kcal
Milk and dairy products					
American cheese	0.85	282	1,063	3.03	8.02
Cheddar cheese	3.11	100	403	3.11	7.72
Feta cheese	0.82	28	75	2.93	10.93
Hard goat cheese	0.45	28	128	1.61	3.75
Part skim ricotta	1.66	124	171	1.34	9.7
Swiss cheese	1.11	28	107	3.96	10.37
Meats					
Beef (composite)	6.8	100	300	6.8	22.67
Lamb (composite)	6	100	288	6	19.98
Roast pork	3.5	100	250	3.5	14
Veal	4	100	250	4	16
Brains (composite)	1.6	100	160	1.6	10
Chitterlings	5.06	100	303	5.06	16.7
Beef heart	3.13	100	175	3.13	17.88
Braised beef liver	6.07	100	191	6.07	31.78
Beef tongue	4.8	100	283	4.8	16.96
Bear meat	10.27	100	259	10.27	39.65
Water buffalo	2.54	100	131	2.54	19.39
Roasted deer	2.75	100	158	2.75	17.4
Cooked eel	1.77	85	201	2.08	8.81
Stewed wild rabbit	2.38	100	173	2.38	5.78
Bratwurst	1.47	70	226	2.1	6.5
Chorizo	2.05	60	273	3.41	7.5
Bologna	0.5	23	72	2.14	6.94
Salami	0.5	23	60	2.17	8.33
Seafood					
Cooked carp	1.26	85	138	1.48	9.13
Swordfish	1.25	85	132	1.46	9.46
Fried clams	1.24	85	172	1.44	7.21
Steamed clams	2.32	85	126	2.72	18.41
Steamed king crab	6.48	85	82	7.62	79.02
Crab cake	2.45	60	93	4.08	26.34
Steamed crayfish	1.26	85	74	1.48	17.02
Atlantic herring	1.08	85	173	1.27	6.24
Steamed lobster	2.48	85	83	2.92	29.88
Cooked octopus	2.86	85	139	3.36	20.57
Perch	1.22	85	100	1.44	12.2
Atlantic oysters	77.35	85	59	91	124.58
Breakfast cereals					
Typical ready-to-eat cereals	3.75	33	120	11.25	31.25
Grains and grain products					
Whole-grain bread	0.33	26	65	1.26	5.07
Pumpernickel	0.47	32	80	1.46	5.88
American rye	0.36	32	83	1.12	4.34
Whole wheat	0.54	28	69	1.93	7.82
Buckwheat pancakes	0.35	30	62	1.17	5.64
Hominy	1.68	160	115	1.05	14.61
Corn tortillas	1.8	100	200	1.8	9

continued

TABLE 4. Foods containing 1.0 mg or more of zinc per 100 g of edible portion *(continued)*

Food	Zn content of standard portion (mg)	Weight of standard portion (g)	Energy value of standard portion (kcal)	Zn content of edible portion	
				mg/100 g	mg/1000 kcal
Carnation breakfast bar	3.75	36	150	10.41	25
Kellogg nutri-grain bar	1.5	37	136	4.05	11.03
Kellogg pop tarts	0.6	52	204	1.15	2.94
Soups					
Chunky beef soup	2.64	240	170	1	15.52
Nuts, seeds, and legumes					
Adzuki beans	4.07	230	294	1.77	13.84
Refried beans	2.96	253	238	1.17	12.43
Pork and beans	3.79	253	281	1.5	13.49
Garbanzo beans	2.51	164	269	1.53	9.33
Red kidney beans	1.89	177	225	1.06	8.4
Baby lima beans	1.87	182	229	1.02	4.37
Pinto beans	1.85	171	234	1.08	7.9
Tofu	0.83	17	82	4.88	10.12
Tempeh	1.5	83	165	1.8	9.1
Natto	3.03	88	187	3.03	14.28
Miso	3.32	138	284	3.32	16.13
Sweets and miscellaneous					
Chocolate chips	4.57	168	1351	2.72	3.38
Canola bar	3.07	87	470	3.52	6.53
Peanuts	0.75	40	208	1.88	3.6
Hershey bar	1	91	471	1.09	2.12
Kit kat wafer	0.42	42	219	1	1.92
Peanut m&m	0.66	49	253	1.34	2.61
Mr. Goodbar	0.88	49	252	1.79	3.49
Peanut butter cup	0.7	50	270	1.4	2.59
Beef jerky	1.62	20	110	8.1	14.72
Potato chips	0.31	28	152	1.1	2.04
Tortilla chips	0.43	28	142	1.54	3.03
Nachos, cheese	1.79	113	346	1.58	5.17

Sources: refs. 73, 109.

breastfed infants of distinct ages, which would allow one to estimate typical zinc intakes by infants. Infants up to three months would be expected to receive about 0.35 mg/kg/day [79]. Actual observed zinc intakes approximating this value have been confirmed in a myriad of studies with breastfed infants [91–95]. It has recently been shown that maternal infection is not a determinant of the concentration of zinc in milk [96]. Zinc deficiency in breastfed infants was described in the 1970s and in recent case reports in preterm infants [97, 98].

The general conclusion of a series of studies [78, 99–102] is that zinc in milk cannot be increased by supplementation to the mother. The delivery of a zinc supplement directly to exclusively breastfed children would be an alternative strategy. In Finnish infants [103], no benefits on growth were observed. However, preliminary data from a similarly designed intervention in low-income mothers and infants in Guatemala by CeSSIAM suggest that giving 13 mg of zinc daily to infants produced more rapid growth [Gyves P, Mazariegos M, personal communication, 2000].

The content of zinc in artificial formula

The zinc content of most infant formulas is higher than that of breastmilk. *Bowes & Church's Food Values of Portions Commonly Used* [73] lists zinc values per ounce (30 g) for 27 different commercial infant formulas and "human milk fortifiers." The values range from 0.10 to 0.36 mg of zinc per 30 ml in the formulas and from 0.36 to 0.71 mg of zinc per ounce in the fortifiers. Most would not supply the 5 mg of zinc recommended by the National Research Council [15] but would cover the 2.8 mg accepted by Brown et al. [78]. The milk-based infant formulas would be deficient in early infancy—and adequate later—according to the WHO/IAEA standards [62].

Zinc and the weaning period

Since zinc deficiency and other zinc-responsive conditions are most prevalent during the preschool years, zinc sources in the weaning period are important considerations. They are reviewed by Brown et al. [78]. Estimated recommendable intakes of zinc for infancy were presented in the foregoing section.

For the second year of life (toddler), the US RDA for zinc is 10 mg. If infants and toddlers were provided with premasticated meat and visceras during most of human evolution, as exemplified by the aboriginal Eskimo, then one can envision achieving this large intake in early life. More modest is the calculation by Brown et al. [78] of a 2.8 mg/day intake of zinc in both the first and the second years of life. For the latter period of the life span, the WHO/IAEA [62] basal requirement, individualized as a daily recommendation, would be 3.1 mg for a high-availability, 5.1 mg for a medium-availability, and 11.8 mg for a low-availability toddler diet.

The task of complementary food in the weaning period is to bridge the gap between what human milk can provide and what is recommended. With its content of around 1.5 mg of zinc per 1,000 kcal of energy in late lactation, the complementary foods in the weaning period must be of high zinc density and superior zinc bioavailability to compensate for the relative deficiency of zinc in human milk.

One theoretical generalization may be made. If it is important to maximize the amount of breastmilk in the weaning transition diet [78, 104] and to preserve the consumption of the traditional staple foods of the culture [105], then the margin for introducing adequate amounts of bioavailable zinc into the diet of the older infant and toddler is extremely narrow, and great ingenuity would be required to accomplish this. Brown et al. [78] undertook the exercise shown in table 5. They divided the dietary transition period into three periods (6–8 months, 9–11 months, and 12–23 months) during which the infant or toddler's diet should still contain some breastmilk. The authors indicated the amounts of specific zinc-rich foods that would be needed to complement the diminishing zinc contribution from maternal milk and meet their required intake of 2.8 mg, within the constraints of the energy allotments from complementary foods of 180, 300, and 500 kcal/day, in the respective age brackets. Adjusting this to actual developing-country settings, they used experience in Mexican and Peruvian children to find out if the required intakes had ever been achieved. The conclusion was generally negative.

Consuming adequate zinc becomes even more dif-

TABLE 5. Examples of zinc-rich foods needed to meet zinc requirements from complementary foods, according to age group

Age (mo)	6–8			9–11			12–23		
$kcal_{th}$ limit[a] Required Zn in complementary foods (mg/day)	180 2.2			300 2.3			500 2.4		
Candidate Zn foods[b]	g	kcal	max g[c]	g	kcal	max g[c]	g	kcal	max g[c]
Beef liver	49	58	—	51	61	12	53	63	72
Pork liver	55	58	—	58	60	—	60	63	76
Chicken liver	69	80	36	72	83	60	75	87	15
Fish, dried	42	142	1	44	148	—	46	155	0
Beef, lean	61	77	7	64	81	25	67	84	103
Cheese, fresh				177	244	3	185	255	121
Fish, sardines				100	193	—	104	201	110
Oats				74	285	56	77	297	20
Milk, powdered				55	202	98	57	210	96
Fish, carp				153	199	86	160	208	96
Pork with bone				121	269	—	126	280	182
Beans				209	265	—	218	277	125
Beef, high-fat with bone				110	255	—	114	260	94
Egg							218	330	65
Milk, fresh							600	396	390
Milk, evaporated							300	402	205
Chicken							171	369	149

a. kcal limit = ⅔ of total average energy required from complementary foods at each age.
b. Candidate foods are all those that contain the required amount of nutrient in less than the kilocalorie limit.
c. Max = maximum grams of that food per day ever consumed by a child in Peru (6–11 mo) or Mexico (12–23 mo).
Source: ref. 78.

ficult when other considerations are introduced. In fact, no more than 30% of the energy should ever come from the "special transitional foods" when breastmilk is maximized. Milk alone or a combination of milk and "family foods" contributes 70% of the energy. Milk is zinc-dilute, and family food in developing-country populations would have low zinc content and poor zinc bioavailability. This puts an almost impossible burden on any subset of foods selected to bridge the zinc gap for the infant or toddler. The WHO/IAEA [62] recommendations for low-bioavailability situations might be more realistic than the flat 2.8 mg/day recommendation of Brown et al. [78] for the toddler in the societies of greatest vulnerability and public health interest. Ironically, as a greater portion of energy intake comes from nonbreastmilk sources during the weaning transition, the chances for the provision of recommended amounts of zinc to the infant in a mixed diet become more favorable.

Hence, it is enlightening to examine the zinc intake of the specialized foods from commercial baby foods, as listed in the "Infant, Junior & Toddler Foods" section of *Bowes & Church's Food Values of Portions Commonly Used* [73]. Table 6 provides the roster of the foods that had more than 1 mg of zinc per 100 g of edible product. Only two items in the meals, but virtually all of the individual meats, met the criterion. The latter had variable but higher densities of zinc based on the energy content of the food. All of the other classes of foods had no representatives that were zinc-dense on a weight basis. However, some foods had an appreciable content of zinc on an energy basis, while failing to meet the weight criterion.

TABLE 6. Sources of zinc in commercial infant, junior, and toddler foods: items containing 1.0 mg or more of zinc per 100 g of edible portion

Food	Zn content	
	mg/100 g	mg/1000 kcal
Baked products	None	None
Cereals	None	None
Desserts	None	None
Dinners		
Gerber Graduates, diced carrots, and white turkey	1.33	23.5
Gerber Graduates, peas and diced chicken	1.08	12.2
Fruit juices	None	None
Fruits	None	None
Meat products		
Beef	2.03–2.95	18.85–27.63
Chicken	1.01–1.40	5.4–10.5
Ham	1.71–2.24	13.54–20.18
Lamb	1.89–3.36	10.3–36.76
Pork	2.27	18.3
Turkey	1.80–2.25	10.1–20.0
Veal	2.01–2.50	19.8–22.8
Vegetables	None	None

Source: ref. 73.

A number of cereal products had large amounts of zinc in 1,000 kcal of edible portion, including oatmeal with apples and cinnamon (13.4 mg), mixed cereal with apples and bananas (11.3 mg), oatmeal with applesauce and bananas (10.6 mg), and rice cereal with applesauce (10.2 mg). There are zinc-rich dinner choices based on 1,000 kcal of energy: toddler beef stew (17.1 mg), vegetable and turkey (14.8 mg), carrots and beef (13.4 mg), macaroni and beef (10.9 mg), turkey stew (10.4 mg), and vegetable and beef (9.5 mg). In the vegetable category, creamed spinach (13.0 mg) and creamed peas (9.3 mg) provided substantial amounts of zinc per 1,000 kcal of product. Although these foods are beyond the economic means of poor families in developing countries, they illustrate how little room there is to maneuver in the introduction of substantial, natural sources of zinc to fill the gap between the two classes of zinc-poor options (late-lactation breastmilk and traditional staples). Without fortification, cereals and paps cannot make up the zinc deficit from the second semester of infancy into the toddler year, when maximal energy intake is provided by human milk.

Zinc in the adult diet

One generic conclusion is that, in most traditional settings, beginning with complementary feeding while the child is still receiving breastmilk and continuing to complete weaning, the preschool child eats from the same cooking pot or meal dishes laid out for the whole family, although not necessarily all of the same items in adult proportions. Anthropologists have studied issues of intrahousehold food distribution [106, 107] to determine the extent to which foods and nutrients from the same larder and the same cooking pot are evenly or differentially distributed to individuals of different sexes and generations within the household. For the policy and programmatic issues in public health nutrition, there is a special interest in three groups: preschool children, pregnant women, and lactating mothers. Each of these groups has different physiological requirements for zinc [15, 62]. In addition, factors associated with poverty, ill health, and tropical environments influence locality-specific requirements for zinc [108].

Similarly, culture and custom may allow for pregnant and lactating women to consume relatively more or less of certain items at a meal than other members of the family group. The margin to intervene and alter this differential distribution of items within a meal through informal and nonformal education has not been fully explored.

In 1976, WHO published its first-ever attempt at a factorial appraisal of the requirements for absorption of zinc and for the RDAs to achieve them [61]. It concluded that a pregnant woman needed to absorb 5.4 mg of zinc daily. In a developing-country diet with low bioavailability of zinc (10%), the intake would have to be 54 mg of zinc per day. This would require impossible amounts of foods available to the poor (see table 4). For example, if we assume equal portions of adzuki beans and hominy grits, 3,176 g of the mixture would be required, providing 1,950 kcal from beans and 1,940 kcal from hominy, for a total of 3,890 kcal.

Hence, when the population consumes tuber-based staples such as potatoes, yams, sweet potatoes, or cassava (manioc), the problem will be consumption of too small an amount to supply sufficient zinc. When the staple is a whole grain such as maize, millet, sorghum, or wheat, the fiber and phytic acid will reduce the bioavailability of what would seem to be important intakes of the metal. Milling and refining, however, will transform the staple cereal into a zinc-poor source. For the huge fraction of humanity that depends on white rice as its staple food, low intakes of zinc and other trace elements are a problem. Legumes contain abundant amounts of zinc in their seed coats, along with large amounts of the inhibitor, phytic acid, resulting in low zinc availability. Traditional beverages based on coffee beans or tea leaves are poor sources of zinc and good sources of inhibiting polyphenols (tannins).

Adventitial "contamination" of the diet with zinc

Chemical elements in the vessels in which foods and beverages are stored, cooked, and consumed can be imparted to the contents. Krause et al. [109] in Guatemala observed an increase in the zinc content of tortillas, depending upon the form of milling and grinding of the dough. Galvanized metals are rarely used in cookware or serving dishes, but at some points during processing and preparation, contacts with zinc alloys may occur.

Practicalities of consumption of zinc-rich foods: Health concerns and other considerations

An important paradigm that was absent until the 1990s enters the discussion of nutrients and nutrient availability for developing countries: the health-promoting or health-prejudicing constituents in food. Cereal- and tuber-based diets are most protective against both cardiovascular disease and cancer, in part because they displace the saturated fats in animal products [110]. The consumption of red meats has also been implicated in the origins of a number of cancers [111]. The foods richest in zinc (table 4) would also be those capable of promoting chronic disease. The nutrition transition is the situation in which poor populations still suffer nutrient deficiencies while the incidence of chronic diseases associated with dietary excesses increases [112]. For this reason, we cannot disregard the chronic disease implication of dietary recommendations, even for developing countries.

Fortification of food with zinc

There is limited information on the bioavailability of the different zinc compounds used for food fortification. Zinc fortification has been recently reviewed [18, 19, 113]. As shown in table 4, zinc is now routinely added to ready-to-eat breakfast cereals and sometimes to other products sold in the United States. Ranum in this issue describes newly initiated cereal fortification programs in Indonesia and Mexico. He indicates that zinc oxide is the preferred source of zinc, because it is inexpensive and produces less flavor change than zinc acetate and zinc sulfate [113].

Fortification of water with zinc

Zinc salts have a bitter, metallic taste, not unlike that of iron. However, in flavored beverages or when diluted with large quantities of water, this taste becomes imperceptible. Dutra et al. [114] explored placing iron salts in the drinking water of preschool children in Ribeirao Prieto, Brazil. At a more community-wide level, the experience with slow-release iodine modules in the wells of Sudanese villages [115] might be a model for zinc in community water supplies.

Practical consequences

Squeezing more zinc into the diet

The food-based solution for increasing the intake of zinc aims at either increasing the intake of zinc-rich foods or improving the zinc density of foods, through food technology or agrarian techniques. As discussed, there are many limitations to increasing the consumption of zinc by changing the selection of food items consumed. Moreover, most of the foods with a high natural content of zinc (meat and seafoods) are too costly for poor families.

Getting more zinc into edible plant food through technological interventions is potentially more feasible. This can be attempted either at the level of cultivation (fertilizers, genetic modification) or at the level of processing or meal preparation (fortification). It requires no change in the pattern of foods consumed, and the additional cost to the consumer might be modest. Since the overall biological availability will still be low, however, only an incremental contribution to net absorbed zinc will occur.

Recent work in plant genetics by the US. Environmental Protection Agency has resulted in "metal-scavenging" plants. A severe practical limitation to their application is that few soils anywhere have lead and cadmium contents so low that the plants will not concurrently take up toxic amounts of these heavy metals. For use as human foods, these plants have to be cultivated by expensive hydroponic methods in which only the nutrient elements are added to the water.

Fortification of foods with zinc by the US food industry has begun to have an impact (table 4). Ready-to-eat cereals and granola-based bars are among the most zinc-dense of all food sources. To the extent that cereals are consumed with milk, with its calcium, and are consumed as high-fiber sources by adults, there will be some attenuation of their bioavailability. A racial gulf might be expected between white and nonwhite Americans if the impact of ready-to-eat cereals on folic acid intake is a guide [116], since nonwhites tend to consume smaller quantities of breakfast cereals.

Enhancing the absorption of zinc

Zinc might be a candidate for measures that would enhance its uptake in foods [13]. However, a specific variety of red wine is the only demonstrated enhancer of zinc absorption [47], hardly suitable for young children or pregnant and lactating women. Reducing inhibitors of zinc absorption is an alternative.

Addressing the phytic acid content of the diet has more promise. Milling of cereal grains reduces the phytate content, which is contained in the seed coat; it also decreases the zinc content of the seed. Soaking grains and legumes (in which the phytate is in the cotyledons) causes activation of intrinsic phytases and represents a "practical, nonenzymic, household method to reduce phytic acid content of certain cereals (e.g., maize) and most legumes, including soybeans"[18]. Germination requires more time, more specific conditions, and consideration of the culinary aspects [18]. It activates endogenous phytases and hydrolyzes phytic acid. Fermentation of cereal dough is a third level of pre-preparatory treatment, which requires starter cultures of lactic acid bacteria and 16 to 24 hours of anticipation.

Application of exogenous phytase to reduce the content of the most important inhibitory substance is a further possibility. As reviewed by Bedford and Schultze [117], the use of phytases in animal fodder for monogastric animals, notably in pork production, has been a successful practice to liberate nutrients and improve growth. This can be accomplished in vitro with human foods [118], as confirmed by Layrisse et al. [119]. One of the treatment groups was a maize arepa, prepared from dough preincubated with reagent-grade phytase, and it showed enhanced iron uptake in experimental subjects. In vivo application of phytase, i.e., oral preparations of the enzyme taken with meals, analogous to beta-galactoses in lactose maldigesters [120], has not yet been explored. Consuming phytase with a legume or an unrefined cereal meal might be effective. Consuming less coffee or tea with meals is theoretically an efficacious measure. Creating low-tannin varieties of tea leaves and coffee beans should be considered.

Genetically modified seeds that produce less phytic acid could be created by transgenic or crossbreeding methods. In fact, a maize with a 40% to 60% reduction in phytate has been developed [121]. It has been examined with respect to iron absorption [122]. Currently, in Guatemala, in a collaboration between the University of Colorado and CeSSIAM, we are examining the effect of reducing the phytate content of the corn used in tortillas on the homeostasis of zinc. The evolutionary value of phytate for the plant as a phosphate-storage mechanism, and perhaps for its protective functions against the pathogens and predators of the plants, should be considered, since low-phytate varieties may have lower crop yields.

Possible benefit of the poor absorption of zinc

Schneider in 1977 at the Institute of Nutrition of Central America and Panama (INCAP) may have been the first to perform a placebo-controlled intervention trial of oral zinc sulfate for the treatment of diarrheal disease [123]. His hypothesis was that zinc acts as an "antiseptic" for the intestine. In this case, the unabsorbed zinc would be available for local, topical effects in the lower gut and the large bowel.

Nutritionists feel that 15 mg of zinc daily is the recommended dietary intake [15], and toxicologists feel that 21 mg of zinc is the highest safe level of oral exposure [14]. One way to harmonize these two conclusions would be to find that the intestine provides a degree of regulation for the entry of zinc, as it obviously does for iron. Too much compensatory promotion of the uptake of zinc into the body might counteract evolutionary down-regulation of this mechanism.

Low zinc exposure and adaptation in the agricultural era

The adverse consequences of high, chronic zinc consumption for nutrient–nutrient interactions that produce deficiency of another related metal are well recognized [22]. The classical example of an adverse consequence of chronic high zinc intake is copper deficiency. More recently, Donangelo et al. [45] reported that in nonanemic young women receiving 22 mg of zinc daily as a supplement over six weeks, there was a significant decrease in iron nutriture, as judged by lower ferritin concentration and an increase in total iron-binding capacity, zinc protoporphyrin, and transferrin receptor status.

Summary and epilogue

An analysis of the actual content of zinc in foods and its bioavailability should cause reexamination of the generally accepted recommended dietary intakes and physiological requirements for humans. To the extent that we adapted metabolically and genetically to the hunter-gatherer diet, the 12 to 15 mg of zinc intake recommended for adults today was probably obtainable from the diet of antiquity. However, in the agricultural era, with a primary dependency on foods of plant origin, the probability of consuming these amounts of zinc became remote. Fortification of foods such as ready-to-eat cereals and bread is a demonstrated way to increase zinc density. Manipulating the phytate content of the diet by in vivo (plant genetics) or in situ (oral phytases) interventions, combined with creating low-tannin tea leaves and coffee beans, might improve absorption of the zinc in meals.

The above considerations lead to a series of queries. There is a unitarian hypothesis abroad that one achieves the growth-promoting and the anti-infective properties of zinc by reversing the underlying zinc deficiency of populations. Since assessing underlying zinc status is a near impossibility [11, 12], the preintervention status of populations in intervention studies is generally uncertain. In this regard, it is interesting to return to the classic 1973 treatise by Sandstead [124], in which he speaks of "zinc-responsive" conditions, begging the question of whether a systemic zinc-depletion state is a precondition to a favorable response to zinc. Some situations improve when supplemental doses of zinc are administered. It may do a disservice to potential beneficiaries to agonize as to whether or not they are zinc-deficient before considering them targets for zinc-intervention programs.

A rule-of-thumb as to whether a supplement of zinc is in the physiological (dietary) or the pharmacological (drug-effect) range is whether we find examples in the course of human evolution of cuisines providing these amounts in a single meal. A supplemental dose of zinc commonly used in recent intervention trials has been 20 mg/day [125–127]. Although 2 to 3 g of Atlantic oyster would provide this amount of zinc, no other usual combination of foods consumed in a single setting would do so. It would take 200 g of bear meat or 300 g of steamed lobster to place 20 mg of zinc into the intestinal tract in a single meal. It would take 1.1 kg of maize tortillas to provide 20 mg of zinc, and this would be of very low biological availability.

With these considerations in mind, one must be cautious in projecting that the zinc-responsive effects of zinc supplements will be duplicated by any combination of zinc-rich foods and zinc-fortified items. This query can—and should—be addressed by appropriately designed and controlled community-based trials in which single-dose zinc supplements, zinc supplements accompanied by a balanced amount of companion micronutrients, and equivalent amounts of zinc from food and beverage sources are compared. Whether we launch into widespread zinc interventions sooner or later, numerous fundamental and operational questions remain to be resolved, and the research agenda for zinc sources and zinc bioavailability is substantial.

References

1. Eaton SB, Konner M. Paleolithic nutrition: a consideration of its nature and current implications. N Engl J Med 1985;312:283–9.
2. Brand-Miller JC, Colagiuri S. Evolutionary aspects of diet and insulin resistance. In: Simopoulos AP, ed. Evolutionary aspects of nutrition and health: diet, exercise, genetics and chronic disease. World Rev Diet Nutr 1999;84:74–105.
3. Simoons FJ. Primary adult lactose intolerance and the milking habit: a problem in biological and cultural interrelations. A cultural historical hypothesis. Am J Dig Dis 1970;15:695–710.
4. Cordain L. Cereal grains: humanity's double-edged sword. In: Simopoulos AP, ed. Evolutionary aspects of nutrition and health: diet, exercise, genetics and chronic disease. World Rev Diet Nutr 1999;84:19–73.
5. Prasad AS, Halsted JA, Nadimi M. Syndrome of iron deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism and geophagia. Am J Med 1961;31:532–46.
6. Halsted JA, Ronaghy HA, Abadi P, Haghshenass M, Amirhakimi GH, Barakat RM, Reinhold JG. Zinc deficiency in man. The Shiraz experiment. Am J Med 1972; 53:277–84.
7. Prasad AS, Miale A, Farid Z, Schulert A, Sandstead HH. Zinc metabolism in patients with the syndrome of iron deficiency anemia, hypogonadism and dwarfism. J Lab Clin Med 1963;61:537–49.
8. Berg A. The nutrition factor. Cambridge, Mass, USA: MIT Press, 1968.
9. Black RE. Therapeutic and preventive effects of zinc on serious childhood infectious diseases in developing countries. Am J Clin Nutr 1998;68:467S–79S.
10. Underwood BA. Micronutrient malnutrition. Is it being eliminated? Nutr Today 1998;33:121–9.
11. Solomons NW. On the assessment of zinc and copper nutriture in man. Am J Clin Nutr 1979;32:856–71.
12. King JC. Assessment of zinc status. J Nutr 1990;120: 1474–9.

13. Solomons NW, Bulux J. Increased nutrient uptake in developing countries through increased bioavailability. Eur J Clin Nutr (suppl) 2001 (in press).
14. Mertz W, Abernathy CO, Olin SS, eds. Risk assessment of essential elements. Washington, DC: International Life Sciences Institute Press, 1994.
15. National Research Council. Recommended dietary allowances. 9th ed. Washington, DC: National Academy of Science Press, 1989.
16. Castenmiller JJM, West CE. Bioavailability and bioconversion of carotenoids. Annu Rev Nutr 1998;18:19–38.
17. Chesters JK. Biochemistry of zinc in cell division and tissue growth. In: Mills C, ed. Zinc in human biology. London: Springer-Verlag, 1989:109–18.
18. Gibson RS, Ferguson EL. Nutrition intervention strategies to combat zinc deficiency in developing countries. Nutr Res Rev 1998;11:115–31.
19. Davidsson L. Zinc. In: Hurrell R, ed. Mineral fortification of foods. Surrey, UK: Leatherhead Food Research Association, 1999:187–97.
20. Sandström B. Dietary pattern and zinc supply. In: Mills CF, ed. Zinc in human biology. New York: Springer-Verlag, 1989:351–63.
21. Sandström B, Arvidsson B, Cederblad Ä, Bjorn-Rasmussen E. Zinc absorption from composite meals. I. The significance of wheat extraction rate, zinc, calcium, and protein content in meals based on bread. Am J Clin Nutr 1980;33:739–45.
22. Solomons NW, Rosenberg IH. Physiological and pathophysiological mechanisms in mineral absorption. In: Solomons NW, Rosenberg IH, eds. Absorption and malabsorption of mineral nutrients. New York: Alan R. Liss, 1984:1–14.
23. Solomons NW, Jacob RA, Pineda O, Viteri FE. Studies on the bioavailability of zinc in man. II. Absorption of zinc from organic and inorganic sources. J Lab Clin Med 1979;94:335–43.
24. Castillo-Duran C, Solomons NW. Studies on the bioavailability of zinc in humans. VIII. Plasma-zinc response to cooked beef. Nutr Res 1991;11:419–27.
25. Solomons NW, Cousins RJ. Zinc. In: Solomons NW, Rosenberg IH, eds. Absorption and malabsorption of mineral nutrients. New York: Alan R. Liss, 1984:125–97.
26. Oelshlegel FJ, Brewer GJ. Absorption of pharmacological doses of zinc. In: Brewer GJ, Prasad AS, eds. Zinc metabolism: current aspects in health and disease. New York: Alan R. Liss, 1977;299–316.
27. Turnland JR, King JC, Keyes WR, Gong B, Michel MC. A stable isotope study of zinc absorption in young men: effects of phytate and cellulose. Am J Clin Nutr 1982; 40:1071–7.
28. Knudsen E, Sandström B, Solgaard P. Zinc, copper and magnesium absorption from a fibre-rich diet. J Trace Elem Med Biol 1996;10:68–76.
29. Reddy MB, Love M. The impact of food processing on the nutritional quality of vitamins and minerals. Adv Exp Med Biol 1999;459:99–106.
30. O'Dell BL. Effect of dietary components upon zinc bioavailability. Am J Clin Nutr 1969;22:1315–22.
31. Lönnerdal B. Dietary factors influencing zinc absorption. J Nutr (suppl) 2000;130:1378S–83S.
32. Golden MH, Golden BE. Effect of zinc supplementation on the dietary intake, rate of weight gain and energy cost of tissue deposition in children recovering from severe malnutrition. Am J Clin Nutr 1981;34:900–8.
33. Lönnerdal B, Cederblad A, Davidsson L, Sandström B. The effect of individual components of soy formula and cow`s milk formula on zinc bioavailability. Am J Clin Nutr 1994;40:1064–70.
34. Reinhold JF, García JS. Fiber in maize tortilla. Am J Clin Nutr 1979;32:1326–32.
35. Kratzer FH, Allred JB, Davis PH, Marshall BJ, Vohra P. The effect of autoclaving soybean protein and the addition of ethylenediaminetetraacetic acid on the biological availability of dietary zinc for turkey poults. J Nutr 1959;68:313–22.
36. Davidsson L, Kastenmayer P, Hurrell RF. Sodium iron EDTA (NaFe(III)EDTA) as a food fortificant: the effect on the absorption and retention of zinc and calcium in women. Am J Clin Nutr 1994;60:231–7.
37. Solomons NW. Competitive interactions of iron and zinc in the diet: consequences for human nutrition. J Nutr 1986;116:927–35.
38. Péres J-M, Bouhallab S, Petit C, Bureau F, Maubois J-L, Arhan P, Bougle D. Improvement of zinc intestinal absorption and reduction of zinc/iron interaction using metal bound to the caseinophosphopeptide 1–25 of β-casein. Reprod Nutr Dev 1998;38:465–72.
39. Sandström B, Davidsson L, Cederblad Ä, Lönnerdal B. Oral iron, dietary ligands and zinc absorption. J Nutr 1985;115:411–4.
40. Davidsson L, Almgren A, Sandström B, Hurrell RF. Zinc absorption in adult humans: the effect of iron fortification. Br J Nutr 1995;74:417–25.
41. Castillo-Duran C, Solomons NW. Studies on the bioavailability of zinc in humans. IX. Interaction of beef-zinc with iron, calcium and lactose. Nutr Res 1991;11:429–38.
42. Hill CH, Matrone G. Chemical parameters in the study of in vivo and in vitro interactions of transition elements. FASEB Proc 1970;29:1474–81.
43. Pollack S, George JM, Reba RC, Kaufman RM, Crosby WH. The absorption of nonferrous metals in iron deficiency. J Clin Invest 1965;4:1470–3.
44. Hambidge KM, Krebs NF, Jacobs MA, Favier A, Guyette L, Ickle DN. Zinc nutritional status during pregnancy: a longitudinal study. Am J Clin Nutr 1983;37:429–42.
45. Donangelo CM, Woodhouse LR, Mertz SD, Viteri FE, King JC. Effect of zinc supplementation on iron metabolism in young women with low iron reserves. FASEB J 2000;14:A483.
46. Krebs NF. Impact of physiologic state on bioavailability of nutrients: infants, children and adolescents. J Nutr (suppl) 2001 (in press).
47. MacDonald JT, Margen S. Wine versus ethanol in human nutrition. IV. Zinc balance. Am J Clin Nutr 1980;33:1096–102.
48. Evans GW, Johnson PE. Characterization and quantification of a zinc-binding ligand in human milk. Pediatr Res 1980;12:876–80.
49. Lönnerdal B, Stanislowski AG, Hurley LS. Isolation of a low molecular weight zinc binding ligand from human milk. J Inorg Biochem 1980;12:71–8.

50. Weigand E, Kirchgessner M. Total true efficiency of zinc utilization: determination and homeostatic dependence upon the zinc supply status in young rats. J Nutr 1980; 110:469–80.
51. Fung EB, Ritchie LD, Woodhouse LR, Roehl R, King JC. Zinc absorption in women during pregnancy and lactation: a longitudinal study. Am J Clin Nutr 1997; 66:80–8.
52. Smith JC Jr. Heritable hyperzincemia in humans. Prog Clin Biol Res 1977;14:181–91.
53. Moynahan EJ. Acrodermatitis enteropathica: a lethal inherited human zinc deficiency disorder. Lancet 1974; 2:399–401.
54. Solomons NW. Biological availability of zinc in humans. Am J Clin Nutr 1982;35:1048–75.
55. Solomons NW. Pathways to impairment of nutritional status by gastrointestinal pathogens, with emphasis on protozoal and helminthic parasites. Parasitology 1993; 107(suppl):S19–S35.
56. Ruz M, Solomons NW. Fecal excretion of exogenous zinc during oral rehydration therapy for acute diarrhea: nutritional implications. J Trace Elem Exp Med 1995; 7:89–100.
57. Heinrich HC, Gabbe EE, Bartels H, Oppitz KH, Bender-Götze CH, Pfau AA. Bioavailability of feed iron-(^{59}Fe), vitamin B12-(^{60}Co) and protein bound selenomethionine-(^{73}Se) in pancreatic exocrine insufficiency due to cystic fibrosis. Klin Wochenschr 1977;55:595–601.
58. Sturniolo GC, Montino C, Rossetto L, Martin A, D'Inca R, D'Odorico A, Naccarato R. Inhibition of gastric acid secretion reduces zinc absorption in man. J Am Coll Nutr 1991;10:372–5.
59. Serfaty-Lacrosniere C, Wood RJ, Voytko D, Saltzman JR, Pedrosa M, Sepe TE, Russell RM. Omeprazole-induced hypochlorhydria does not affect intestinal absorption of calcium, phosphorus, magnesium or zinc from food in humans. J Am Coll Nutr 1995;14:364–8.
60. Pekarek RS, Evans GW. Effect of leukocyte endogenous mediator (LEM) on zinc absorption in the rat. Proc Soc Exp Biol Med 1976;152:573–5.
61. World Health Organization. Trace elements in human nutrition. Geneva: WHO, 1976.
62. World Health Organization/International Atomic Energy Agency. Trace elements in human health and nutrition. Geneva: WHO, 1995.
63. Monsen EL, Hallberg L, Layrisse M, Hegsted DM, Cook JD, Mertz W, Finch CA. Estimation of available dietary Fe. Am J Clin Nutr 1978;31:134–41.
64. Fitzgerald SL, Gibson RS, Thompson LU, Quan de Serrano J, Portocarrero L, Vasquez A, Zepeda E, Lopez CY, Solomons NW. Trace element intakes and dietary phytate/Zn and Ca × phytate/Zn millimolar ratios of peri-urban Guatemalan women during the third trimester of pregnancy. Am J Clin Nutr 1993;57:195–201.
65. Oberleas D, Harland BF. Phytate content of foods: effects on dietary zinc availability. J Am Diet Assoc 1981; 79:433–6.
66. Gibson RS. Zinc nutrition in developing countries. Nutr Res Rev 1994;7:151–73.
67. Bindra GS, Gibson RS, Thompson LU. [Phytate] [calcium]/[zinc] ratios in Asian immigrant lacto-ovo vegetarian diets and their relationship to zinc nutriture. Nutr Res 1986;6:475–83.
68. Cossack ZT, Prasad AS. Effect of protein source on the bioavailability of zinc in human subjects. Nutr Res 1983;3:23–31.
69. Cook JD, Dassenko SA, Whittaker P. Calcium supplementation: effects on iron absorption. Am J Clin Nutr 1991;53:106–11.
70. Hallberg L, Brune MM, Erlandsson M, Sandberg A-S, Rossander-Hultén L. Calcium: effect of different amounts on nonheme- and heme-iron absorption in humans. Am J Clin Nutr 1991;53:112–9.
71. Matseshe JW, Phillips SF, Malagelada J-R, McCall JT. Recovery of dietary iron and zinc from the proximal intestine of health man: studies of different meals and supplements. Am J Clin Nutr 1980;33:1946–53.
72. Solomons NW, Shrimpton R. Zinc. In: Warren KS, Mahmoud, eds. Tropical and geographic medicine. New York: McGraw-Hill 1983:1059–63.
73. Pennington JAT. Bowes & Church's food values of portions commonly used. 17th ed. Philadelphia: Lippincott, 1998.
74. McCance RA, Widdowson EM. Mineral metabolism of healthy adults on white and brown bread dietaries. J Physiol 1942;101:44–56.
75. Sandström B, Cederblad A, Lönnerdal B. Zinc absorption from human milk, cow's milk and infant formulas. Am J Dis Child 1983;137:726–9.
76. Krebs NF, Hambidge KM. Zinc requirements and zinc intakes of breastfed infants. Am J Clin Nutr 1986;43:288–92.
77. Krebs NF. Zinc homeostasis in breastfed infants. Pediatr Res 1996;39:661–5.
78. Brown KH, Dewey KG, Allen LH. Complementary feeding of young children in developing countries: a review of current scientific knowledge. Geneva: WHO, 1998.
79. Picciano MF, Guthrie HA. Copper, iron, and zinc contents of mature human milk. Am J Clin Nutr 1976; 29:242–54.
80. Arnaud J, Favier A. Copper, iron, manganese and zinc contents in human colostrum and transitory milk of French women. Sci Total Environ 1995;159:9–15.
81. Bates CJ, Tsuchiya H. Zinc in breast milk during prolonged lactation: comparison between the UK and the Gambia. Eur J Clin Nutr 1990;44:61–9.
82. Bates CJ, Prentice A. Breast milk as a source of vitamins, essential minerals and trace elements. Pharm Ther 1994;62:193–220.
83. Casey CE, Hambidge KM, Neville MC. Studies in human lactation: zinc, copper, manganese and chromium in human milk in the first month of lactation. Am J Clin Nutr 1985;41:1193–2000.
84. Casey CE, Neville MC, Hambidge KM. Studies in human lactation: secretion of zinc, copper, and manganese in human milk. Am J Clin Nutr 1989;49:773–85.
85. Feeley RM, Eitenmiller RR, Jones JB, Barnhart H. Copper, iron, and zinc contents of human milk at early stages of lactation. Am J Clin Nutr 1983;37:443–8.
86. Frkovic A, Medugorac B, Alebic-Juretic A. Zinc levels in human milk and umbilical cord blood. Sci Total Environ 1996;192:207–12.
87. Lehti KK. Breast milk folic acid and zinc concentrations of lactating, low socio-economic, Amazonian women and the effect of age and parity on the same two nutrients. Eur J Clin Nutr 1990;44:675–80.

88. Ohtake M, Tamura T. Changes in zinc and copper concentrations in breast milk and blood of Japanese women during lactation. J Nutr Sci Vitaminol 1993; 39:189–200.
89. Vaughan LA, Weber CW, Kemberling SR. Longitudinal changes in the mineral content of human milk. Am J Clin Nutr 1979;32:2301–6.
90. World Health Organization/International Atomic Energy Agency. Minor and trace elements in breast milk. Report of a joint WHO/IAEA collaborative study. Geneva: WHO, 1989.
91. Butte NF, Garza C, Smith E, Wills C, Nichols B. Macro- and trace mineral intakes of exclusively breast-fed infants. Am J Clin Nutr 1987;15:42–8.
92. Krebs NF, Hambidge KM. Zinc requirements and zinc intake of breast-fed infants. Am J Clin Nutr 1985; 41:571–7.
93. Krebs NF, Reidinger C, Robertson AD, Hambidge KM. Growth and intakes of energy and zinc in infants fed human milk. J Pediatr 1994;124:32–9.
94. Michaelsen KF, Samuelson G, Graham TW, Lönnerdal B. Zinc intake, zinc status and growth in a longitudinal study of healthy Danish infants. Acta Paediat 1994; 83:1115–21.
95. Sievers E, Oldigs HD, Dörner K, Schaub J. Longitudinal zinc balances in breast-fed and formula-fed infants. Acta Paediat 1992;81:1–6.
96. Lönnerdal B, Zavaleta B, Kusunoki L, Lanata CF, Peerson JM, Brown KH. Effect of postpartum maternal infection on proteins and trace elements in colostrum and early milk. Acta Paediat Scand 1996;85:537–42.
97. Heinen F, Matern D, Pringsheim W, Leititis JU, Brandis M. Zinc deficiency in exclusively breastfed preterm infant. Eur J Pediatr 1995;154:71–5.
98. Obladen M, Kampmann W, Renz H. Zinc deficiency in rapidly growing preterm infants. Acta Paediatr 1998;87:685–91.
99. Vuori E, Mäkinen SM, Kara R, Kuitunen P. The effects of the dietary intakes of copper, iron, manganese, and zinc on the trace element content of human milk. Am J Clin Nutr 1980;33:227–31.
100. Krebs NF. Zinc supplementation during lactation. Am J Clin Nutr 1998;68 (suppl):509S–12S.
101. Krebs NF, Hambidge KM, Jacobs MA, Rasbach JO. The effects of a dietary zinc supplement during lactation on longitudinal changes in maternal zinc status and milk zinc concentrations. Am J Clin Nutr 1985;41:560–70.
102. Krebs NF, Reidinger CJ, Hartley S, Robertson AD, Hambidge KM. Zinc supplementation during lactation: effects on maternal status and milk zinc concentrations. Am J Clin Nutr 1995;61:1030–6.
103. Salmenperä L, Perheentupa J, Näntö V, Siimes MA. Low zinc intake during exclusive breast-feeding does not impair growth. J Pediat Gastroenterol Nutr 1994;18: 361–70.
104. Caulfield L, Huffman SL, Piwoz EG. Interventions to improve intake of complementary foods by infants 6 to 12 months of age in developing countries: Impact on growth and on the prevalence of malnutrition and potential contribution to child survival. Food Nutr Bull 1999;20:183–200.
105. Sharma I. Trends on intake of ready-to-eat foods among school children in Nepal. SCN News 1998;16:21–2.
106. Gittlesohn J. Opening the box. Intrahousehold food allocation in rural Nepal. Soc Sci Med 1991;33:1141–54.
107. Kaiser LL, Dewey KG. Household economic strategies, food resource allocation, and intrahousehold patterns of dietary intake in rural Mexico. Ecol Food Nutr 1991; 25:123–46.
108. Solomons NW, Ruz M. Trace element requirements in humans. An update. J Trace Elem Exp Med 1998; 11(suppl):177–95.
109. Krause V, Solomons NW, Tucker KL, Lopez CY, Ruz M, Kuhnlein HV. Rural-urban variation in the calcium, iron, zinc and copper content of tortillas and intake of these minerals from tortillas by women in Guatemala. Ecol Food Nutr 1992;28:289–97.
110. Willett WC. Convergence of philosophy and science: the Third International Congress on Vegetarian nutrition. Am J Epidemiol 1999;70(suppl):434S–8S.
111. World Cancer Research Foundation/American Institute of Cancer Research. Diet, nutrition and prevention of cancer. A global perspective. London: WCRF, 1997.
112. Popkin BM. The nutrition transition in low income countries. An emerging crisis. Nutr Rev 1995;51:285–95.
113. Ranum P. Zinc enrichment of cereal staples. Food Nutr Bull 2001;22:169–72.
114. Dutra de Oliveira JE, Ferriera JF, Vasconcellos VP, Marchini JS. Drinking water as an iron carrier to control anemia in preschool children in a day-care center. J Am Coll Nutr 1994;13:198–202.
115. Elnagar B, Eltom M, Anders-Karlsson F, Bourdoux PP, Gebre-Medhin M. Control of iodine deficiency using iodination of water in a goitre endemic area. Int J Food Sci Nutr 1997;48:113–8.
116. Cuskelly GJ, McNutly H, Scott JM. Fortification with low amounts of folic acid makes a significant difference in folate status in young women: implications for the prevention of neural tube defects. Am J Clin Nutr 1999; 70:234–9.
117. Bedford MR, Schulze H. Exogenous enzymes for pigs and poultry. Nutr Res Rev 1998;11:91–114.
118. Svanberg U, Lorri W, Sandberg AS. Lactic fermentation of non-tannin and high-tannin cereals: effects on in vitro estimation of iron availability and phytate hydrolysis. J Food Sci 1993;58:408–12.
119. Layrisse M, García-Casal MN, Solano L, Barón MA, Argüello F, Llovera D, Ramírez J, Leets I, Tropper E. Vitamin A reduces the inhibition of iron absorption by phytates and polyphenols. Food Nutr Bull 1998; 19:3–5.
120. Rosado JL, Solomons NW, Lisker R, Bourges H. Enzyme replacement therapy for primary adult lactase deficiency: effective reduction of lactose-malabsorption and milk intolerance by direct addition of beta-galactosidases to milk at mealtime. Gastroenterology 1984;87:1072–82.
121. Raboy V, Gerbasi P. Genetics of myo-inositol phosphate synthesis and accumulation. In: Biswas BB, Biswas B, eds. Subcellular biochemistry, myo-inositol phosphates, phosphoinositides, and signal transduction. Vol 26. New York: Plenum Press, 1996:257–85.
122. Mendoza C, Viteri F, Lönnerdal B, Young KA, Raboy V, Brown KH. Effects of genetically-modified, low-phytic acid maize on absorption of iron from tortillas. Am J Clin Nutr 1998;68:1123–7.

123. Schneider RE. Efectos de la administración oral diaria de sulfato de zinc sobre la frecuencia de diarrea no específica, flora fecal y concentración de hidógeno espirado a las 6 a.m. en niños. Informe Annual de INCAP. Guatemala City: Institute of Nutrition of Central America and Panama, 1978.
124. Sandstead HH. Zinc nutrition in the United States. Am J Clin Nutr 1973:26:1251–60.
125. Rosado JL, Lopez P, Muñoz E, Martinez H, Allen LH. Zinc supplementation reduced morbidity, but neither zinc nor iron supplementation affected growth or body composition of Mexican preschoolers. Am J Clin Nutr 1997;65:13–9.
126. Roy SK, Tomkins AM, Mahalanabis D, Akramuzzaman SM, Haider R, Behrens RH, Fuchs G. Impact of zinc supplementation on persistent diarrhoea in malnourished Bangladeshi children. Acta Paediatr 1998;87:1235–9.
127. Sazawal S, Black BE, Bhan MK, Ghandari N, Sinha A, Jalla S. Zinc supplementation in young children with acute diarrhea in India. N Engl J Med 1995;33:839–44.

Zinc deficiency, immune function, and morbidity and mortality from infectious disease among children in developing countries

Robert E. Black

Abstract

Zinc deficiency is prevalent in developing countries and has adverse effects on child health. Decreased or abnormal immune function in children can occur as a consequence of zinc deficiency, either during gestation or after delivery, and may impair host defenses against infectious diseases. Controlled trials of therapy of acute and persistent diarrhea have consistently demonstrated that zinc-supplemented children have diarrheal episodes of shorter duration and reduced severity. Controlled trials of zinc supplementation in the prevention of infectious diseases have demonstrated reductions in the incidences of diarrhea, pneumonia, and malaria, the most common causes of death in children in developing countries. Preliminary evidence from one controlled trial in full-term small-for-gestational-age infants in India found a two-thirds reduction in mortality with zinc supplementation. In conclusion, zinc deficiency reduces immune function and increases the risk of morbidity and mortality from infectious disease in children in developing countries.

Introduction

Deficiency of the trace element zinc may be more widespread and have greater effects on the health of infants and children than previously realized. It has been well recognized that severe deficiency, as in acrodermatitis enteropathica, has many manifestations, including failure to thrive, thymic atrophy, severe depression of immunity, and diarrhea [1]. It has only been recognized more recently that mild to moderate zinc deficiency may present clinically as impaired growth, which may have previously been attributed to other factors [2]. Effects of mild to moderate zinc deficiency on immune function and the risk of infectious diseases in children in developing countries have also been demonstrated [3]. These relationships are the subject of this review.

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Gestational zinc deficiency and immune function after birth

Gestational zinc deficiency has been studied in a number of animal models, including mice and nonhuman primates. Even with mild levels of zinc deficiency during gestation, there is a reduction in lymphoid tissue, especially manifest as atrophy of the thymus, and a reduction in immunoglobulin concentrations in the blood of the newborn [4–7]. Additionally, there appears to be more specific suppression of particular immunoglobulins, such as IgM, IgA, and some subtypes of IgG, which might affect the immunologic protection in early infancy from systemic bacterial infections [8, 9]. There may also be alterations in the function of the cellular elements, such as lymphocytes and neutrophils [7]. Evidence from animal studies suggests that these abnormalities present at birth can be long-lasting or even permanent. In fact, some evidence suggests that this immunocompromise can persist even to second- or third-generation offspring of animals deprived of adequate zinc during gestation [10].

Studies in humans are limited but suggest similar immunologic consequences of zinc deficiency during gestation. In trials of zinc supplementation during pregnancy, children of zinc-supplemented mothers have greater immunoglobulin concentrations and reduced rates of infectious disease during infancy [3]. Additional studies are under way to determine whether zinc supplementation in pregnancy in a presumably zinc-deficient population enhances the immune response to vaccines in infancy.

Zinc deficiency and immune function

The defenses against infection are particularly sensitive to disturbances in zinc status. The barrier functions of the skin [1], as well as those of the pulmonary and gastrointestinal tracts [11], are damaged, and the development, function, or both of most immunologic cells suffer deleterious effects [3].

The human immune system is quite sensitive to zinc deficiency. Among the cellular elements that are affected, natural killer cells have reduced activity [12], polymorphonuclear leukocytes have impaired chemotactic responses and microbicidal function [13, 14], and macrophages or monocytes have impaired chemotactic responses, reduced phagocytosis, and reduced intracellular killing of microorganisms [15, 16].

The development of T lymphocytes is profoundly altered by zinc deficiency, with a reduction in the size and cellularity of the thymus and depletion of lymphocytes from the spleen, lymph nodes, and peripheral blood in animal models [12, 17]. Zinc-deficient humans have reduced total numbers of lymphocytes, especially T lymphocytes, in the blood and peripheral lymphoid tissue [18–20]. Decreased CD4+/CD8+ cell ratios are also seen [21]. These abnormalities in humans can be reversed by administration of supplemental zinc. T-lymphocyte function is also altered in zinc deficiency, with a reduction in delayed hypersensitivity responses and cytotoxic activity, which are reversed by zinc supplementation in humans [12, 18–22]. Other studies have shown that zinc deficiency alters T-lymphocyte activation and proliferation and may reduce the response to antigens (and potentially even to vaccines, especially those requiring T-cell–dependent antibody production) [23, 24].

The development of B lymphocytes in the bone marrow is also adversely affected by zinc deficiency, with a reduction in both number and function [25, 26]. Antibody responses are inhibited by zinc deficiency, with abnormalities in mitogenic and cytokine responses; however, T-cell–dependent antibody responses seem to be more affected than T-cell–independent responses [27, 28]. Little is know about the effects of zinc deficiency on secretory immunity or other local mucosal host defenses.

In animal models, there is a reduction in the activity of thymulin and altered release of cytokines, and an imbalance of cell-mediated and antibody-mediated immunity may occur, even with mild levels of zinc deficiency [29–31].

The applicability of all of the studies of zinc deficiency in animal models to human health is unclear, but immunocompromise in humans with mild zinc deficiency has been demonstrated, with the abnormalities reversing with small quantities of additional zinc [17, 32]. The rapidity of response in these functions to repletion of zinc varies, but some functions, such as intracellular killing by macrophages, are restored very rapidly with supplementation [15]. Additional studies are needed on the level of functional abnormalities with differing degrees of zinc deficiency and the correlation of these abnormalities with susceptibility to specific infectious diseases.

Effects of zinc supplementation on therapy of diarrhea

The therapeutic effects of zinc supplementation during diarrhea have been investigated in five trials of acute diarrhea and five trials of persistent diarrhea [33–38]. These studies show consistent benefits of zinc supplementation. In the studies of acute diarrhea (duration on enrollment in these studies ranged from less than three days to more than seven days) (table 1), zinc supplementation generally resulted in shorter diarrheal episodes and a reduced likelihood that the episode would continue for more than seven days after enrollment in the study. With the small sample size in some of these studies, not all of the apparent effects were statistically significant. A pooled analysis of zinc supplementation in acute diarrhea trials for which original data could be obtained (three trials) revealed an overall 15% (95% confidence interval, 5% to 24%) reduced probability of continuing diarrhea in the supplemented group [33]. A meta-analysis of all five trials found a statistically significant effect size of 0.162 (table 2) [33]. Several of the studies also reported reductions in episode severity, as measured by frequency of watery stools or measured stool output (table 1).

The trials of treatment of persistent diarrhea (episodes lasting for more than 14 days) likewise showed benefits with zinc supplementation (table 3) [33, 39–43]. Generally, the studies found that supplementation was associated with a shorter episode duration. The pooled analysis involving four of these trials indicated that children had a 24% (95% confidence interval, 9% to 37%) reduced probability of continuing diarrhea if they received the zinc supplement [33]. A meta-analysis of all five trials found a statistically significant summary effect size of 0.293 (table 4) [33]. There was also a suggestion of reduced episode severity in one trial, but not in a second trial (table 3). Importantly, though, most trials reported large reductions in the rate of treatment failure or death (table 3). Overall, in the pooled analysis, there was a 42% (95% confidence interval, 10% to 63%) reduced rate of treatment failure or death in children given zinc supplements [33].

Subgroup analyses were performed by age (< 12 months vs ≥ 12 mo), wasting (< –2 Z vs ≥ –2 Z weight-for-height), and sex [33]. For acute diarrhea, each of the subgroups had statistically significant benefits of zinc supplementation. For persistent diarrhea, the subgroups of < 12 months wasted and male had statistically significant effects; their corresponding alternatives had smaller beneficial effects that were not statistically significant.

TABLE 1. Trials evaluating the therapeutic effects of zinc supplementation on acute diarrhea

Country	No. in Zn/control groups	Enrollment: Age (mo)	Enrollment: Nutritional criteria	Zn supplement	Control supplement	Effect of Zn on episode duration	Effect of Zn on no. of episodes > 7 days	Effect of Zn on episode severity
India [34]	25/25	6–18	Excluded moderate to severe malnutrition	20 mg as sulfate	Placebo	9.4% shorter episodes	—	18.2% lower stool frequency
India [35]	456/481	6–35	Excluded severe malnutrition	20 mg as gluconate; vitamins A,B,D,E	Vitamins A, B, D, E	21.3% reduced probability of continuing diarrhea[a]	15% fewer	39% fewer watery stools[a]
Bangladesh [36]	57/54	3–24	Included if weight-for-age < 76th percentile	20 mg as acetate; vitamins A,B,D,E	Vitamins A,B,D,E	14.5% reduced probability of continuing diarrhea	23% fewer[a]	28% lower stool output
Bangladesh [37]	343/341	6–23	Excluded severe malnutrition	14 or 40 mg as acetate; vitamin C; half with vitamin A	Vitamin C; half with vitamin A	20% reduced probability of continuing diarrhea[a]	43% fewer[a]	—
Indonesia [38]	739/659	3–25	None	4–5 mg/kg	Placebo as acetate	11%	28% fewer shorter episodes[a]	—

a. Statistically significant ($p < .05$) effect.

TABLE 2. Meta-analysis of the therapeutic effects of zinc supplementation on the mean duration of acute diarrhea

Trial	Zinc group	Control group	Effect size (95% confidence interval)	*p*
	Mean ± SD			
India [34]	3.4 ± 1.8	3.8 ± 1.7	0.199 (–0.357, 0755)	0.50
India [35]	4.5 ± 3.6	5.4 ± 3.4	0.238 (0.109, 0.367)	< 0.01
Bangladesh [36]	5.1 ± 2.5	5.5 ± 2.7	0.122 (–0.269, 0.513)	0.54
Bangladesh [37]	6.1 ± 5.1	7.1 ± 5.1	0.178 (0.028, 0.329)	0.03
Indonesia [38]	3.5 ± 2.4	3.8 ± 2.6	0.096 (–0.010, 0.201)	0.08
Summary estimate			0.162 (0.068, 0.2560)	

Effects of zinc supplementation on prevention of infectious diseases

Zinc deficiency has been associated with higher rates of infectious diseases, including skin infections, diarrhea, respiratory infections, and malaria, as well as with delayed wound healing. With regard to effects in developing countries, the most studied have been diarrhea and lower respiratory infections, although limited information on malaria is also available [44–50]. Because of the difficulty in assessing the zinc status of children in a population, most information on the effect of zinc deficiency on the risk of infectious disease comes from randomized, controlled trials of zinc supplementation. In these trials, when zinc is the only experimental variable, there is direct causal evidence that additional zinc can result in lower rates of infectious diseases.

Seven trials of zinc supplementation provide information on outcomes of diarrhea, and four of these provide information on pneumonia (table 5). Most trials were performed with preschool children who were typical of poor developing-country populations, but two studies selected more poorly nourished children. These trials were done in seven different countries, representing a wide range of social and economic development and nutritional status.

The results with regard to diarrheal incidence are

TABLE 3. Trials evaluating the therapeutic effects of zinc supplementation on persistent diarrhea

Country	No. in Zn/control groups	Enrollment		Zn supplement	Control supplement	Effect of Zn on episode duration	Effect of Zn on episode severity	Effect of Zn on treatment failure or death
		Age (mo)	Nutritional criteria					
India [39]	20/20	6–18	Excluded moderate to severe malnutrition	20 mg as acetate	Placebo	18.9% shorter episodes	21.4% lower stool frequency	
Bangladesh [40]	95/95	3–24	None	20 mg as acetate	Vitamins A, B, D	15.3% reduced probability of continuing diarrhea	—	63% reduction[a]
Peru [41]	139/136	6–35	None	20 mg as gluconate	Placebo	18% reduced probability of continuing diarrhea	—	19% reduction
Pakistan [42]	43/44	6–36	Weight-for-age ≤ –2Z	3 mg/kg as sulfate; vitamins A, B, D, E	Vitamins A, B, D, E	2.0% reduced probability of continuing diarrhea	No effect	58% increase
Bangladesh [43]	44/44	6–24	Weight-for-age < 76th percentile	20 mg as acetate; vitamins B, C, D; half with vitamin A	Vitamins B, C, D; half with vitamin A	55% reduced probability of continuing diarrhea[a]	—	75% reduction[a]

a. Statistically significant ($p < .05$) effect.

TABLE 4. Meta-analysis of the therapeutic effects of zinc supplementation on the mean duration of persistent diarrhea

Trial	Zinc group	Control group	Effect size (95% confidence interval)	*p*
	Mean ± SD			
India [39]	3.7 ± 1.1	3.8 ± 2.6	0.530 (–0.101, 1.160)	0.20
Bangladesh [40]	6.5 ± 3.7	7.0 ± 3.8	0.135 (–0.199, 0.470)	0.42
Peru [41]	2.2 ± 1.7	3.0 ± 2.5	0.360 (0.051, 0.670)	< 0.03
Pakistan [42]	5.1 ± 3.3	5.5 ± 2.7	0.122 (0.408, 0.652)	0.66
Bangladesh [43]	2.9 ± 1.4	3.5 ± 1.4	0.421 (–0.059, 0.901)	0.13
Summary estimate			0.293 (0.060, 0.525)	

consistent in showing that zinc-supplemented children have lower rates of diarrhea than control children. Most of these studies individually found statistically significant differences in diarrheal incidence, and a pooled analysis showed that overall the incidence of diarrhea in zinc-supplemented children was 18% (95% confidence interval, 7% to 28%) less than in unsupplemented children [51]. Since it also appears that zinc supplements reduce the duration of diarrhea, it is not surprising that the overall effect in the pooled analysis on the prevalence of diarrhea was greater than the effect on incidence, i.e., a 25% (95% confidence interval, 12% to 37%) lower prevalence of diarrhea in the zinc-supplemented children.

In subgroup analyses, there was a statistically significant pooled effect of zinc on diarrheal incidence among children 12 months of age or older (fig. 1), but no significant effect in the younger children (fig. 2). With regard to nutritional status, both subgroups (< –2 Z vs ≥ –2 Z weight-for-age) had statistically significant pooled effects of zinc on diarrheal incidence (figs. 3 and 4). The effects were similar for boys and girls, although that for girls was statistically significant and that for boys was of borderline significance. Only two studies contributed to the subgroup analyses by plasma zinc status (< 60 vs ≥ 60 fg/dl), so the data were limited. There was a trend toward a benefit of zinc supplementation on the incidence of diarrhea in

TABLE 5. Trials evaluating the therapeutic effects of zinc supplementation on prevention of diarrhea or pneumonia

Country	No. in Zn/ control groups	Child-years		Enrollment		Zn supplement	Control supplement	Effect of Zn on incidence of diarrhea	Effect of Zn on incidence of pneumonia
		Zn	Control	Age (mo)	Other criteria				
Vietnam [44]	73/73	30.8	30.8	4–36	Weight-for-age and height-for-age < –2Z	10 mg as sulfate	Placebo	44% less[a]	44% less[a]
India [45, 46]	286/293	122.9	124.8	6–35	Recovered from acute diarrhea	10 mg as gluconate; vitamins A, B, D, E	Vitamins A,B,D,E	8% less	43% less[a]
Mexico [47]	97/97	116.0	117.1	18–36	—	20 mg as methionate; half with iron	Placebo; half with iron	37% less[a]	—
Guatemala [48]	45/44	23.2	22.9	6–9	—	10 mg as sulfate	Placebo	18% less[a]	—
Jamaica [49]	31/30	7.1	6.2	6–24	Weight-for-age < –2Z	5 mg as sulfate; vitamins A, B, C, D	Vitamins A,B,C,D	8% less	88% less
Peru [41]	80/79	36.1	37.4	6–35	Recovered from persistent from diarrhea	10 mg as gluconate	Placebo	12% less[a]	15% less
Papua New Guinea [50]	136/138	75.3	80.7	6–60	—	10 mg as gluconate	Placebo	12% less	—

a. Statistically significant ($p < .05$) effect.

both subgroups, which was larger in the group with lower plasma zinc, but the effect was not statistically significant in either group [51].

Four studies provide information on the effects of zinc supplementation on the incidence of pneumonia [41, 44, 46, 49]. These studies consistently showed that zinc-supplemented children had lower rates of pneumonia, and two of these studies showed sizable and statistically significant effects individually [44, 46]. The other two studies had smaller numbers, and the differences did not reach statistical significance [41, 49]. Overall, in the pooled analysis, there was a 41% (95% confidence interval, 17% to 59%) lower rate of pneumonia in zinc-supplemented children [51].

Only two randomized, controlled trials provide information on the effects of zinc supplementation on clinical attacks of malaria. In the Gambia, with a twice-weekly 70-mg zinc supplement, there was a 46% reduction in clinic visits due to malaria, which was of only borderline statistical significance in this small study [52]. In a larger trial with daily zinc supplementation using 10 mg of elemental zinc as gluconate in Papua New Guinea, there was a statistically significant reduction of 40% in *Plasmodium falciparum* malaria clinic-based attack rates, and a higher efficacy (70%) for clinical attacks with parasite densities of more than 100,000/μl of blood [50].

Effects of zinc supplementation on child mortality

Pneumonia and diarrhea are the two most common causes of death in children in developing countries, and malaria also contributes substantially to mortality in many settings. With the large and consistent effects of zinc supplementation on the incidence and, in some cases, severity of these infectious diseases, one might hypothesize an effect also on child mortality. None of the studies of zinc supplementation done to date have been of sufficient size to fully address the effects on mortality. One recent study in India provides preliminary evidence that zinc-supplemented infants have a lower rate of overall mortality [53]. In this trial, among 1,250 small-for-gestational-age infants studied from one to nine months of age, there was

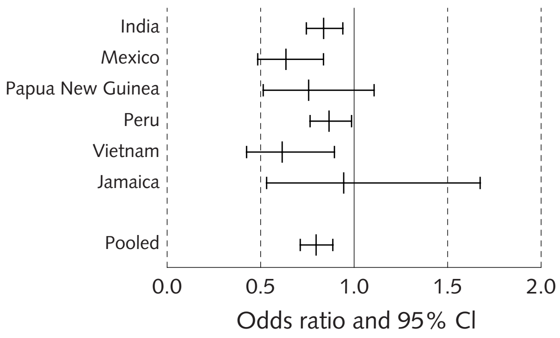

FIG. 1. Preventive effect of zinc supplementation on diarrheal incidence in continuous supplementation trials in children 12 months or more of age [51]

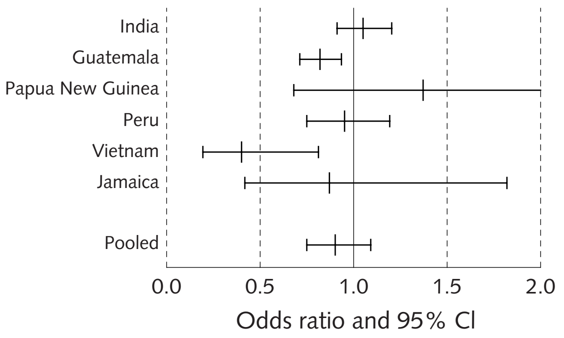

FIG. 2. Preventive effect of zinc supplementation on diarrheal incidence in continuous supplementation trials in children less than 12 months of age[51].

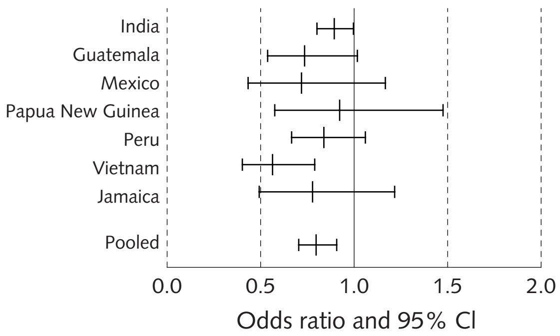

FIG. 3. Preventive effect of zinc supplementation on diarrheal incidence in continuous supplementation trials in children with weight-for-age Z-score < –2 [51].

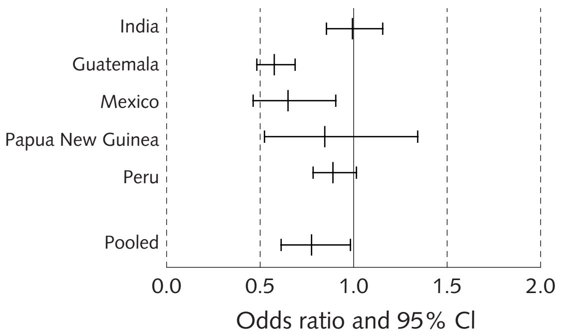

FIG. 4. Preventive effect of zinc supplementation on diarrheal incidence in continuous supplementation trials in children with weight-for-age Z-score ≥ –2 [51].

a 67% reduction in mortality in zinc-supplemented infants. Supplementation with selected other vitamins and minerals, including iron, was not associated with a significant reduction in mortality in this four-cell factorial design trial.

Conclusions

It is clear that zinc deficiency compromises many immune functions, although the direct relationship of these abnormalities to recovery from or risk of infectious diseases is not clear. However, there is now evidence that zinc supplementation can improve the outcomes of acute and persistent diarrhea and can prevent attacks of diarrhea and pneumonia, as well as possibly malaria. It is important to confirm these findings, especially those for pneumonia and malaria, for which results from diverse settings are limited. Additionally, it is important to evaluate the effects of zinc supplementation on child mortality in potentially vulnerable developing-country populations. Plans are under way to conduct such trials in three settings—Zanzibar, India, and Nepal—and these studies should start within the next year. In the meantime, it appears that there is ample reason to consider public health applications using zinc either therapeutically or preventively. The therapeutic uses of zinc during diarrhea need further evaluation, particularly from the standpoint of testing feasible modes of delivery. For the preventive uses of zinc, there is need to explore various alternative ways to improve zinc nutriture of children in developing countries. These include improving the dietary quantity and bioavailability of zinc, fortifying foods with zinc, and providing supplements, perhaps in combination with iron and other micronutrients.

References

1. Aggett P. Severe zinc deficiency. In: Mills C, ed. Zinc in human biology. London: Springer-Verlag, 1989:259–79.
2. Brown K, Peerson J, Allen L. Effect of zinc supplementation on children's growth: a meta-analysis of intervention trials. Bibl Nutr Dieta 1998;54:76–83.
3. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. Am J Clin Nutr 1998;68(suppl):447S–63S.
4. Beach RS, Gershwin ME, Hurley LS. Reversibility of developmental retardation following murine fetal zinc deprivation. J Nutr 1982;112:1169–81.
5. Beach RD, Gershwin ME, Hurley LS. Persistent immunological consequences of gestational zinc deprivation. Am J Clin Nutr 1983;38:579–90.
6. Keller PR, Fraker PJ. Gestational zinc requirement of the A/J mouse: effects of a marginal zinc deficiency on in utero B cell development. Nutr Res 1986;6:41–50.
7. Haynes DC, Gershwin ME, Golub MS, Cheung AT, Hurley LS, Hendricks AG. Studies of marginal zinc deprivation in rhesus monkeys: VI. Influence on the immunohematology of infants in the first year. Am J Clin Nutr 1985;42:252–62.
8. Kearney JF, Bartles J, Hamilton AM, Lehuen A, Solvason J, Vakil M. Development and function of the early B cell repertoire. Int Rev Immunol 1992;8:247–57.
9. Vakil M, Kearney JF. Functional relationship between T15 and J558 idiotypes in BALB/c mice. Dev Immunol 1991;1:213–24.
10. Beach RS, Gershwin ME, Hurley LS. Gestational zinc deprivation in mice: persistence of immunodeficiency for three generations. Science 1982;218:469–71.
11. Solomons NW. Zinc and copper. In: Shils ME, Young VR, eds. Modern nutrition in health and disease. 7th ed. Philadelphia: Lea and Febiger, 1988:238–62.
12. Fernandes G, Nair M, Onoe K, Tanaka T, Floyd R, Good RA. Impairment of cell mediated immune functions by dietary Zn deficiency in mice. Proc Natl Acad Sci USA 1979;76:457–61.
13. Weston WL, Huff JC, Humbert JR, Hambridge KN, Neldner KH, Walravens PA. Zinc correction of defective chemotaxis in acrodermatitis enteropathica. Arch Dermatol 1977;13:422–5.
14. Briggs WA, Pedersen M, Mahajan S, Sillix DH, Prasad AS, McDonald FD. Lymphocyte and granulocyte function in zinc treated and zinc deficient hemodialysis patients. Kidney Int 1982;21:827–32.
15. Wirth JJ, Fraker PJ, Kierszenbaum F. Zinc requirements for macrophage function: effect of zinc deficiency on uptake and killing of a protozoan parasite. Immunology 1989;68:114–9.
16. James SJ, Swendseid M, Makinodan T. Macrophage-mediated depression of T-cell proliferation in zinc deficient mice. J Nutr 1987;117:1982–8.
17. Fraker PJ, Gershwin ME, Good RA, Prasad A. Interrelationships between zinc and immune function. Fed Proc 1986;45:1474–9.
18. Oleske JM, Westphal ML, Shore S, Gorden D, Bogden JD, Nathmias A. Zinc therapy of depressed cellular immunity in acrodermatitis enteropathica. Am J Dis Child 1979;133:915–8.
19. Golden MHN, Jackson AA, Golden BE. Effect of zinc on thymus of recently malnourished children. Lancet 1977;2:1057–9.
20. Golden MHN, Golden BE, Harland PSEG, Jackson AA. Zinc and immunocompetence in protein-energy malnutrition. Lancet 1978;1:1226–8.
21. Sazawal S, Jalla S, Mazumder S, Sinha A, Black RE, Bhan MK. Effect of zinc supplementation on cell-mediated immunity and lymphocyte subsets in preschool children. Indian Pediatr 1997;34:589–97.
22. Allen JI, Kay NE, McClain CJ. Severe zinc deficiency in humans: association with a reversible T-lymphocyte dysfunction. Ann Intern Med 1981;95:154–7.
23. Ochi T, Sato K, Ohsawa M. Suppression of the proliferative response of human lymphocytes to cultured allogeneic HeLa cells in zinc. Toxicol Lett 1983;15:225–30.
24. Malave I, Rondon-Benaim I. Modulatory effect of zinc on the proliferative response of murine spleen cells to polyclonal T cell mitogens. Cell Immunol 1984;89:322–30.
25. Fraker PJ, Osatiashtiani E, Wagner MA, King LE. Possible roles for glucocorticoids and apoptosis in the suppression of lymphopoiesis during zinc deficiency: a review. J Am Coll Nutr 1995;14:11–7.
26. Fraker PJ, Telford WG. A reappraisal of the role of zinc in life and death decisions of cells. Proc Soc Exp Biol Med 1997;215:229–36.
27. Luecke RW, Simonel CE, Fraker PJ. The effect of restricted dietary intake on the antibody mediated response of the zinc deficient A/J mouse. J Nutr 1978; 108:881–7.
28. DePauquale-Jardieu P, Fraker PJ. Interference in the development of a secondary immune response in mice by zinc deprivation: persistence of effects. J Nutr 1984; 114:1762–9.
29. Prasad AS, Meftah S, Abdallah J, Kaplan J, Brewer GJ, Bach JF, Dardenne M. Serum thymulin in human zinc deficiency. J Clin Invest 1988;82:1202–10.
30. Dardenne M, Pleau JM, Nabbara B, Lefrancier P, Derrien M, Choay J, Bach JF. Contribution of zinc and other metals to the biological activity of the serum thymic factor. Proc Natl Acad Sci USA 1982;79:5370–3.
31. Flynn A, Loftus MA, Finke JH. Production of interleukin-1 and interleukin-2 in allogeneic mixed lymphocyte cultures, under copper, magnesium and zinc deficient conditions. Nutr Res 1984;4:673–9.
32. Prasad AS, Beck FWJ, Grabowski SM, Kaplan J, Mathog RH. Zinc deficiency: changes in cytokine production and T-cell subpopulations in patients with head and neck cancer in non-cancer subjects. Proc Assoc Am Physicians 1997;109:68–77.
33. Bhutta ZA, Bird SM, Black RE, Brown KH, Gardner JM, Hidayat A, Khatun F, Martorell R, Ninh NX, Penny ME, Rosado JL, Roy SK, Ruel M, Sazawal S, Shankar A (Zinc Investigators' Collaborative Group). Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. Am J Clin Nutr 2000;72:1516–22.
34. Sachdev HPS, Mittal NK, Mittal SK, Yadav HS. A controlled trial on utility of oral zinc supplementation

in acute dehydrating diarrhea in infants. J Pediatr Gastroenterol Nutr 1988;7:877–8.
35. Sazawal S, Black RE, Bhan MK, Ghandari N, Sinha A, Jalla S. Zinc supplementation in young children with acute diarrhea in India. N Engl J Med 1995;333:839–44.
36. Roy SK, Tomkins AM, Akramuzzaman SM, Behrens RH, Haider R, Mahalanabis D, Fuchs G. Randomised controlled trial of zinc supplementation in malnourished Bangladeshi children with acute diarrhoea. Arch Dis Child 1997;77:196–200.
37. Faruque ASG, Mahalanabis D, Haque SS, Fuchs GJ, Habte D. Double-blind, randomized, controlled trial of zinc or vitamin A supplementation in young children with acute diarrhoea. Acta Paediatr 1999;88:154–60.
38. Hidayat A, Achadi A, Sunoto, Soedarmo SP. The effect of zinc supplementation in children under three years of age with acute diarrhea in Indonesia. Med J Indonesia 1998;7:237–41.
39. Sachdev HPS, Mittal NK, Yadav HS. Oral zinc supplementation in persistent diarrhoea in infants. Ann Trop Paediatr 1990;10:63–9.
40. Roy SK, Tomkins AM, Mahalanabis D, Akramuzzaman SM, Haider R, Behrens RH, Fuchs G. Impact of zinc supplementation on persistent diarrhoea in malnourished Bangladeshi children. Acta Paediatr 1998;87:1235–9.
41. Penny ME, Peerson JM, Marin RM, Duran A, Lanata CF, Lönnerdal B, Black RE, Brown KH. Randomized, community-based trial of the effect of zinc supplementation with and without other micronutrients, on the duration of persistent childhood diarrhea in Lima, Peru. J Pediatr 1999;135(2 pt1):208–17.
42. Bhutta ZA, Nizami SQ, Isani Z. Zinc supplementation in malnourished children with persistent diarrhea in Pakistan. Pediatrics 1999;103:1–9.
43. Khatun UHF. Impact of zinc and vitamin A supplementation in malnourished hospitalized children suffering from persistent diarrhoea. Doctoral thesis, University of Dhaka, Institute of Nutrition and Food Science, Dhaka, Bangladesh, July 1998.
44. Ninh NX, Thissen JP, Collette L, Gerard GG, Khoi HH, Ketelslegers JM. Zinc supplementation increases growth and circulating insulin-like growth factor I (IGF-I) in growth-retarded Vietnamese children. Am J Clin Nutr 1996;63:514–9.
45. Sazawal S, Black RE, Bhan MJ, Jalla S, Sinha A, Bhandari N. Efficacy of zinc supplementation in reducing the incidence and prevalence of acute diarrhea—a community-based, double-blind, controlled trial. Am J Clin Nutr 1997;66:413–8.
46. Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A, Bhan MK. Zinc supplementation reduces the incidence of acute lower respiratory infection in infants and preschool children—a double-blind controlled trial. Pediatrics 1998;102:1–5.
47. Rosado JL, Lopez P, Munoz E, Martinez H, Allen LH. Zinc supplementation reduced morbidity, but neither zinc nor iron supplementation affected growth or body composition of Mexican preschoolers. Am J Clin Nutr 1997;65:13–9.
48. Ruel MT, Rivera JA, Santizo MC, Lonnerdal B, Brown KH. Impact of zinc supplementation on morbidity from diarrhea and respiratory infections among rural Guatemalan children. Pediatrics 1997;99:808–13.
49. Gardner JM, Witter MM, Ramdath DD. Zinc supplementation: effects on the growth and morbidity of undernourished Jamaican children. Eur J Clin Nutr 1998;52:34–9.
50. Shankar AH, Genton B, Baisor M, Paino J, Tamja S, Adiguma T, Wu L, Rare L, Bannon D, Tielsch JM, West KP Jr, Alpers MP. The influence of zinc supplementation on morbidity due to *Plasmodium falciparu*m: a randomized trial in pre-school children in Papua New Guinea. Am J Hyg Trop Med 2000;62:663–9.
51. Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, Khatun F, Martorell R, Ninh NX, Penny ME, Rosado JL, Roy SK, Ruel M, Sazawal S, Shankar A (Zinc Investigators' Collaborative Group). Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. J Pediatr 1999;135:689–97.
52. Bates CJ, Evans PH, Dardenne M, Prentice A, Lunn PG, Northrop-Clewes CA, Hoare S, Cole TJ, Horan SJ, Longman SC, Stirling D, Aggett P. A trial of zinc-supplementation in young rural Gambian children. Br J Nutr 1993;69:243–55.
53. Sazawal S, Black RE, Menon VP, Dhingra U, Dhingra P, Mazumder S, Caulfield L, Khosla S. Effect of zinc and mineral supplementation in small for gestational age infants on growth and mortality. FASEB J 1999;13 (4 part 1):A376.

General experience with zinc supplementation: Are we ready for large-scale supplementation programs?

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Abstract

Zinc is an essential nutrient often lacking in children's diets, especially when there is a high prevalence of stunting. Although numerous supplementation trials have been conducted to determine whether zinc deficiency is present in the community, little attention has been devoted to assessing different strategies for providing additional zinc to children. Before starting large-scale zinc-supplementation programs, there are several key issues that need to be addressed, such as the optimal frequency of zinc delivery, possible interactions with other micronutrients, the merits of a food-based approach as compared with supplements, the type of food to fortify, and the effect on the bioavailability of zinc of mixing it with food.

Introduction: assessing the problem of zinc deficiency

Zinc is an essential nutrient found mainly in protein-rich foods. Zinc is often lacking, or present in a poorly absorbable form, in the diet of poor families. Zinc is present in high concentration in plant foods rich in phytate, which may prevent its absorption [1], and in animal products, such as liver or red meat, which are often expensive or not traditionally given to young children [2].

There are no specific clinical signs or biochemical indicators associated with mild zinc deficiency, and the only effect of insufficient intake might be growth retardation in young children or increased morbidity [3]. The first step to assess the risk of zinc deficiency in a community is to estimate intake by dietary survey and to compare actual intakes with recommended values [4]. This approach, however, has limitations. First, the zinc content of local foods is not always known. For example, the zinc content of foods of plant origin varies according to the zinc level in the soil where the plant was grown. Second, there are uncertainties regarding absorption of zinc from phytate-containing foods. Finally, estimates of zinc requirements are not known with precision, as reflected by estimates given by different committees [2, 5, 6]. For these reasons, randomized supplementation trials are usually regarded as the best way to assess the probability of zinc deficiency in a community. In the last 20 years, more than 25 trials have been conducted in various countries. Their results have been reviewed extensively elsewhere [4, 7]. These studies often show a positive impact on growth of children, especially when there is a high prevalence of stunting. Several studies also suggest a reduction of morbidity due to common illnesses, especially diarrhea [8]. An improvement of neuropyschologic development after zinc supplementation has also been reported [9].

The practical implication of these studies is that in many situations, zinc should be provided to children. The rationale for proposing zinc supplementation instead of locally available zinc-rich foods is the low price of zinc compounds compared with these foods. Simple calculations show that the cost of the zinc itself is always very low and is always less than the price of any local food providing the same amount of zinc. The cost of a zinc supplement is related more to the cost of packaging than to the price of zinc itself.

Previously completed supplementation trials were designed as efficacy studies, examining the biological effects of zinc supplementation. For the present review, we reexamined published community-based supplementation studies [4, 7, 9–14] to consider several practical aspects of zinc supplementation. Although these studies strongly suggest that zinc supplementation may have favorable effects, several questions need to be answered before implementing large-scale supplementation programs.

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Physical form of zinc supplements

Zinc can be given in a syrup, a tablet, or a powder mixed directly with food. Syrup is the most expensive form of zinc supplement. Syrups are typically packaged in a bottle containing water, sweetener, and a flavoring agent, making them more expensive than a simple tablet. Tablets cannot be given to children under the age of five years unless they are provided in a self-dissolving form, which also increases the price slightly. Tablets may have an unpleasant taste, especially if they contain a soluble zinc compound. Capsules have the advantage of masking the taste of the zinc compound, but these cannot be swallowed by most small children. However, capsules can be opened and the content mixed with food. Of the 25 studies we reviewed, the majority (16 studies) used syrup to provide the zinc supplement. Notably, this is the form least adaptable to large-scale supplementation because of its higher cost and larger volume, which complicates distribution and storage.

Fortification of food with zinc is presumably the method best adapted to large-scale distribution. This approach is used in industrialized countries to prevent iron and vitamin D deficiencies, which may occur in young children in these settings. Fortification is generally more effective than individual supplementation in preventing sporadic cases. In relief operations, fortifying a widely distributed food is also the most commonly used approach to preventing deficiencies [15]. Surprisingly, only one of the published studies that we reviewed used food as a vehicle for providing zinc to children [16].

Chemical forms of zinc supplements

Zinc compounds used as supplements can be classified as soluble or insoluble zinc salts. Soluble salts can be used to prepare syrups. These soluble salts may have an unpleasant taste and must be given along with sugar or other flavoring agents. When mixed with food, soluble salts must be added in small quantities to avoid taste alteration, although comprehensive sensory trials using different forms of zinc and different foods are still lacking. Insoluble salts have virtually no taste, and zinc oxide, an insoluble, tasteless zinc compound, is most commonly selected by consumers in the United States, where a wide choice of zinc supplements are available [17]. Insoluble salts cannot be incorporated into syrups but are easily mixed with food.

Soluble salts are better absorbed than insoluble salts [18]. This difference seems especially important when gastric acidity is reduced. This may be a factor with malnourished children, who often have reduced gastric acidity [19]. There do not seem to be marked differences in absorption among soluble salts [20].

Most reviewed studies (23 of 25) used soluble salts to test the efficacy of zinc supplements. It is difficult to say whether insoluble salts, though more convenient to use, would be as effective as the soluble compounds used in these studies.

Timing of zinc supplementation in relation to meals

Few studies mentioned the time of day when the zinc supplement was given. It seems likely that these supplements were given separately from meals, since they were often given under supervision by health workers or school teachers. This may have favorably influenced the outcome of the studies. Zinc absorption is clearly superior when zinc is given apart from meals. This may be related to a competition at the absorption site between the zinc given as supplement and endogenous zinc secreted in the lumen in response to a meal [21]. Phytate present in the diet may further reduce the absorption of zinc, as suggested by a study comparing zinc uptake from meals of differing phytate levels [22]. Phytate may play a major role in affecting the absorption of zinc given during meals in developing countries, where diets are often rich in phytate [1].

Dosage of zinc supplements

Since there is no simple indicator of zinc status, zinc requirements are difficult to estimate. For this reason, different committees provide different recommendations (table 1). Formal dose-response studies using different levels of zinc supplements are not yet available. Most of the published studies of zinc supplementation that reported positive results provided 5 to 10 mg of zinc, with no clear advantages of higher levels. Therefore, there is no strong argument to recommend higher levels of supplementation. There is even some evidence that high levels of zinc intake may have an adverse effect on the immune system [23] or on copper status [24]. Zinc doses provided in previous studies were given as soluble salts, in most cases between meals. Therefore, higher levels of supplementation

TABLE 1. Comparison of zinc recommended daily intake (mg/day) according to different committees

Committee	Age (mo) 6–11	Age (mo) 12–36
United States, 1989 [5]	5	10
European Union, 1993 [6]	4	4
WHO, 1998 [2]	2.8[a]	2.8[a]

a. Estimated recommended intakes, assuming 30% bioavailability.

may be needed if insoluble forms of zinc are provided or if the supplement is given with meals.

Frequency of supplementation

The cost of supplements increases with the number of doses required. Therefore, if equally efficacious, it would be advantageous to provide a larger dose at less frequent intervals. In situations where supplements are provided under direct supervision, costs may also be reduced by forgoing daily distribution. Of the 25 reviewed studies, one gave the zinc supplement biweekly [25] and another gave it weekly [14]. The biweekly supplementation had no effect on growth. This negative result may be due to other nutrient deficiencies limiting growth in these subjects or to frequency of distribution. The second study, which compared the efficacy of weekly to daily supplements [14], found a comparable effect of the supplement on growth for both frequencies of distribution. This effect was limited to children who were found to be stunted when enrolled in the study.

Single versus multiple micronutrient supplementation

Diets deficient in zinc are usually diets with few animal products (meat or milk products) and are also often deficient in iron and calcium. The price difference between micronutrients found in foods and those of chemical origin is always largely in favor of the chemical supplements. Therefore, it makes sense to add zinc to the diet as a supplement at the same time as iron and other micronutrients. There is an antagonism between iron and zinc at the absorption level, but this effect is not important when levels close to the daily requirements of both zinc and iron are used. Moreover, this antagonism does not seem to persist when iron and zinc are given during meals [26].

There is also some evidence that other nutrients should be added to zinc and iron in the supplement to increase its efficacy. One of the early studies on zinc supplementation examined the effect of zinc alone, a full supplement with vitamins and minerals excluding zinc, and the same multinutrient supplement including zinc [27]. This study showed a positive effect of zinc when provided with multinutrients, whereas several previous studies, in a similar environment, did not show any effect of zinc supplements alone. The interpretation of these results is that zinc may be ineffective when another key nutrient is missing in the diet. Similar findings have been reported recently in China [9]. A parallel has been made to the role of a missing nutrient in the diet with that of a missing amino acid in a protein [3].

Multiple micronutrient supplements may have an unpleasant taste if some unpalatable nutrients are given in high quantities. They cannot be given in syrup form because of the possible chemical interaction that can take place between some nutrients when present in high concentration in the same solution. For all of these reasons, multiple micronutrient supplements are most conveniently given in a capsule or as a fortificant in a food carrier.

Supplementation using fortified foods targeted at high-risk groups

As described above, supplementation may take the form of a liquid or a tablet, or a powder or sprinkle added directly to foods. By contrast, fortification is the addition of nutrients to a food product during processing. The most straightforward and cost-effective method of providing missing nutrients at the community level is to fortify the staple food [28]. However, this universal fortification might be difficult when the staple food is produced locally or in kitchen gardens, or it may be inappropriate when the levels consumed by the general population are much higher (and could thus reach possibly toxic levels) than those consumed by the target population. Corn-soya blend and Unimix are two examples of fortified processed cereals in wide use in relief operations that are targeted at infants and young children [15]. There are slightly different versions of these products, and the composition of those most commonly used in recent years is shown in table 2.

Blended flours have some limitations as vehicles for multiple micronutrients. However, millions of metric

TABLE 2. Composition and micronutrient content of Unimix, the blended food most widely used in relief operations

Ingredient	% by weight
Whole maize	70
Whole soy beans	25
Sugar	5
Minerals and vitamins	
Micronutrient	**Weight/100 g dry weight**
Vitamin A	390 μg
Vitamin C	30 mg
Thiamin	0.1 mg
Riboflavin	0.4 mg
Vitamin B_{12}	1 μg
Niacin	5 mg
Folic acid	0.05 mg
Calcium	100 mg
Zinc	5 mg
Iron	8 mg

Source: ref. 15.

tons of these products have been distributed in the last 20 years [29]. Although the World Food Programme website provides statistics on commodity distributions by year, there is very little information on their impact on the growth and health of children. These products are usually prepared from whole maize and soy grains, and their phytate content is very high, at least 700 mg per 100 g. Zinc and iron are likely to be poorly absorbed from these foods, and there is clearly a need to account for likely absorption from these products.

The volume of blended food consumed by the target population is also a concern. To be effective as a vehicle for missing micronutrients, at least 100 g of blended food, such as that described in table 2, must be eaten daily by the child, in addition to the usual family diet. This will be difficult to achieve with children who eat only small quantities of these blended foods. Moreover, the cost of such a fortification may be high, given the large quantities of blended food to be consumed by the general population. Various proposals have been made to increase the micronutrient content of these blended flours to increase their efficacy [30, 31]. Although some of these modified blended foods have been widely used in the last five years, there has been no evaluation of their effect on the growth or health of children.

Recently, it has been proposed to bring missing nutrients up to recommended levels by adding fortified foods as a "supplement" targeted at the population group at high risk for deficiency. The concept is derived from the development of a ready-to-use nutrition rehabilitation food [32]. This food is based on the composition of the World Health Organization F100 rehabilitation formula [33] and is very well accepted by children, despite its high content of unpalatable minerals needed for rehabilitation of severely malnourished children. This food, which looks like a spread (similar to peanut butter or a chocolate spread), has very good acceptability, presumably related to its high fat content. From this rehabilitation food, a more concentrated nutrient-dense spread was designed (table 3).

The idea is to add a small quantity of this food to the usual family diet, just to supplement missing nutrients without reducing other nutrients. The formula shown in table 3 was tested in a preliminary trial in stunted anemic children in Algeria using 50-g portions. These portions of nutrient-dense spread contained considerably more micronutrients than 100 g of the most common blended foods (compare tables 2 and 3). These very high fortification levels may not be needed, or indeed may be too high, in a normally nourished population. Smaller quantities than 50 g per day of this highly fortified spread may be given. This first trial showed very good acceptability of this product, a positive impact on linear growth, and a reduction of anemia [34]. These results suggest that a highly fortified minor constituent of the diet, used as a supplement, may be a better option than a fortified food consumed in large quantities.

TABLE 3. Composition of a nutrient-dense spread, prepared from locally available, cheap foods, that may be used to improve the ration of a child[a]

Ingredient	Quantity/100 g
Minerals	
Calcium	1,000 mg
Phosphorus	630 mg
Potassium	1,135 mg
Magnesium	156 mg
Iron	42 mg
Zinc	41 mg
Copper	2 mg
Vitamins	
A	2 mg
C	125 mg
B1	3.5 mg
B2	4 mg
B6	3.5 mg
B12	3.5 μg
Folic acid	0.5 mg

a. Child is to be given 50 g/day.

Future issues for zinc-supplementation programs

It seems unrealistic to implement large-scale supplementation programs on the basis of the small number of completed efficacy studies. It seems likely that programs currently based on syrups will be followed by attempts to use food as a vehicle for providing missing nutrients. More research is needed before implementing these programs. The most important item on the agenda might be to repeat studies of the efficacy of food-based programs, since it should not be taken for granted that doses used in previous studies can be used with this new approach. The type of food to fortify and the optimal frequency of consumption of fortified food should also be carefully examined.

Absorption of zinc and other micronutrients taken during meals may be improved in the near future by adding phytase to the fortified food. This technology is widely used in animals to promote growth but has received little attention for human use. Phytase fit for human consumption is not available, presumably because of lack of demand by nutritionists [35]. Clearly, all aspects of large-scale micronutrient supplementation are not yet solved, and all possible ways to improve present programs must be explored.

References

1. Ferguson EL, Gibson RS, Thompson LU, Ounpuu S, Berry M. Phytate, zinc, and calcium contents of 30 East African foods and their calculated phytate:Zn, Ca:phytate, and [Ca][phytate]/[Zn] molar ratios. J Food Comp Anal 1988;1:316–25.
2. Brown KH, Dewey K, Allen L. Complementary feeding of young children in developing countries: a review of current scientific knowledge. Geneva: World Health Organization, 1998.
3. Golden MH. The nature of nutritional deficiency in relation to growth failure and poverty. Acta Paed Scand 1991;374:95S–110S.
4. Gibson RS. Zinc nutrition in developing countries. Nutr Res Rev 1994;7:151–73.
5. National Research Council. Recommended dietary allowances. Washington, DC: National Academy Press, 1989.
6. Commission of the European Communities. Reports of the scientific committee for food, 31st series. Brussels: Directorate General Industry, 1993.
7. Brown KH, Peerson JM, Allen LH. Effect of zinc supplementation on children's growth: a meta-analysis of intervention trials. Bibl Nutr Dieta 1998;4:76–83.
8. Black RE. Therapeutic and preventive effects of zinc on serious childhood infectious diseases in developing countries. Am J Clin Nutr 998;68:476S–9S.
9. Sandstead HH, Penland JG, Alcock NW, Dayal HH, Chen XC, Li JS, Zhao F, Yang JJ. Effects of repletion with zinc and other micronutrients on neuropsychologic performance and growth of Chinese children. Am J Clin Nutr 1998;68:470S–5S.
10. Bhutta ZA, Nizami SQ, Isani Z. Zinc supplementation in malnourished children with persistent diarrhea in Pakistan. Pediatrics 1999;103:1–9.
11. Kikafunda JK, Walker AF, Allan EF, Tumwine JK. Effect of zinc supplementation on growth and body composition of Ugandan preschool children: a randomized, controlled, intervention trial. Am J Clin Nutr 1998;68:1261–6.
12. Lira PI, Ashworth A, Morris SS. Effect of zinc supplementation on the morbidity, immune function, and growth of low-birth-weight, full-term infants in northeast Brazil. Am J Clin Nutr 1998;68:418S–24S.
13. Rivera JA, Ruel MT, Santizo MC, Lonnerdal B, Brown KH. Zinc supplementation improves the growth of stunted rural Guatemalan infants. J Nutr 1998;128:556–62.
14. Thu BD, Schultink W, Dillon D, Gross R, Leswara ND, Khoi HH. Effect of daily and weekly micronutrient supplementation on micronutrient deficiencies and growth in young Vietnamese children. Am J Clin Nutr 1999; 69:80–6.
15. Toole MJ. Preventing micronutrient deficiency diseases. In: Report of a workshop on the improvement of the nutrition of refugees and displaced people in Africa. Nairobi, Kenya: University of Nairobi, Applied Nutrition Programme, 1995:47–61.
16. Hambidge KM, Chavez MN, Brown RM, Walravens PA. Zinc nutritional status of young middle-income children and effects of consuming zinc-fortified breakfast cereals. Am J Clin Nutr 1979;32:2532–9.
17. Whittaker P. Iron and zinc interactions in humans. Am J Clin Nutr 1998;68:442S–6S.
18. Henderson LM, Brewer GJ, Dressman JB, Swidan SZ, DuRoss DJ, Adair CH, Barnett JL, Berardi RR. Effect of intragastric pH on the absorption of oral zinc acetate and zinc oxide in young healthy volunteers. J Parenteral Enteral Nutr 1995;19:393–7.
19. Gilman RH, Partanen R, Brown KH, Spira WM, Khanam S, Greenberg B, Bloom SR, Ali A. Decreased gastric acid secretion and bacterial colonization of the stomach in severely malnourished Bangladeshi children. Gastroenterology 1988;94:1308–14.
20. Prasad AS, Beck FWJ, Nowak J. Comparison of five zinc preparations in humans using oral zinc tolerance test. J Trace Elem Exp Med 1993;6:109–15.
21. Sian L, Hambidge KM, Westcott JL, Miller LV, Fennessey PV. Influence of a meal and incremental doses of zinc on changes in zinc absorption. Am J Clin Nutr 1993; 58:533–6.
22. Farah DA, Hall MJ, Mills PR, Russell RI. Effect of wheat bran on zinc absorption. Hum Nutr Clin Nutr 1984; 38:433–41.
23. Wellinghausen N, Rink L. The significance of zinc for leukocyte biology. J Leukocyte Biol 1998;64:571–7.
24. Yadrick MK, Kenney MA, Winterfeldt EA. Iron, copper, and zinc status: response to supplementation with zinc or zinc and iron in adult females. Am J Clin Nutr 1989;49:145–50.
25. Bates CJ, Evans PH, Dardenne M, Prentice A, Lunn PG, Northrop Clewes CA, Hoare S, Cole TJ, Horan SJ, Longman SC. A trial of zinc supplementation in young rural Gambian children. Br J Nutr 1993;9:243–55.
26. Sandström B, Davidsson L, Cederblad A, Lönnerdal B. Oral iron, dietary ligands and zinc absorption. J Nutr 1985;115:411–4.
27. Ronaghy HA, Reinhold JG, Mahloudji M, Ghavami P, Fox MR, Halsted JA. Zinc supplementation of malnourished schoolboys in Iran: increased growth and other effects. Am J Clin Nutr 1974;27:112–21.
28. Ranum P. Zinc enrichment of cereal staples. Food Nutr Bull 2001;22:169–72.
29. World Food Programme. Food aid shipments: WFP and global food aid shipments by commodity category, 1996–99 [data base online] Available from: http://www.wfp.org/index.htm, Under: WFP statistics, In: World Food Programme Statistics Page: 1999.
30. Golden MHN, Briend A, Grelety Y. Report of a meeting on supplementary feeding programmes with particular references to refugee populations. Eur J Clin Nutr 1995; 49:137–45.
31. Beaton GH. Fortification of foods for refugee feeding. Final report. Hull, Quebec: Canadian International Development Agency, 1995.
32. Briend A, Lascala R, Prudhon C, Mounier B, Grellety Y, Golden MHN. Ready to use therapeutic food for treatment of marasmus. Lancet 1999;353:1767–8.

33. World Health Organization. Management of severe malnutrition: a manual for physicians and other health workers. Geneva: WHO, 1999.
34. Branca F, Lopriore C, Guidoum Y, Briend A, Golden MH. Multi-micronutrient fortified food reverses growth failure and anaemia in 2–5 year-old stunted refugee children. Proceedings of the 8th European Nutrition Conference, Lillehammer, 17–19 June 1999. Scand J Nutr 2000;43:51S (abstract).
35. Gibson RS, Yeudall F, Drost N, Mtitimuni B, Cullinan T. Dietary interventions to prevent zinc deficiency. Am J Clin Nutr 1998;68(2 suppl):484S–7S.

Zinc enrichment of cereal staples

Peter Ranum

Abstract

General fortification of cereal staples, such as wheat flour and maize meal, has proven to be a cost-effective method to reduce micronutrient deficiencies. Recent recognition of the problem of zinc deficiency has led to its being included in newly started cereal-enrichment programs in Indonesia and Mexico and in a cereal-fortification program being proposed for South Africa. The amount of zinc added in these programs is 20 to 30 ppm. Zinc oxide is currently the preferred source because it has the lowest cost and produces less flavor change than zinc acetate and zinc sulfate. This article reviews the use of different zinc salts as fortificants, considering their possible effects on product quality and bioavailability, recommended levels of fortification with estimated effects on zinc consumption, and current fortification programs with cost estimates.

Introduction

Zinc has risen in importance to join vitamin A, iodine, and iron among the micronutrients whose deficiency problems must be addressed. It has been a generally held belief that zinc deficiencies are rare and predominantly confined to young children in a few developing countries. This belief, along with the difficulty of demonstrating and characterizing a zinc deficiency, has made it difficult to get zinc included in cereal-enrichment programs. There has also been a general resistance to the inclusion of micronutrients in addition to the standard iron, calcium, and the three B vitamins thiamin, riboflavin, and niacin. This thinking has changed somewhat with the recent successful inclusion of folic acid by the United States and Canada in their cereal-enrichment standards as a means to reduce the incidence of neural tube birth defects. There now appears to be sufficient justification for including zinc in most cereal-enrichment programs in developing countries. Cereal-enrichment programs recently started in Indonesia and Mexico include zinc, and a proposed program for South Africa includes zinc as well.

In this paper, the term *enrichment* refers to the addition of micronutrients that were reduced by the milling process to milled cereal staples, whereas *fortification* is a more general term meaning the addition of any nutrient to any type of food, whether or not it was previously naturally present in the food. Since zinc is naturally present in all cereal grains and is reduced by the milling process to a similar extent as iron is reduced, the addition of zinc to milled cereals falls nicely under the term of enrichment. The addition of vitamin A to wheat flour or corn meal would, however, be considered fortification, because vitamin A is not naturally present in large amounts in these cereals. Enrichment programs were originally based on replacing only the amount of a micronutrient that was lost to milling, but they now encompass adding even greater levels of that micronutrient to better achieve adequate dietary intakes. Since this practice increases the levels beyond those that were originally present in the food, it could be considered a type of fortification. This excess "enrichment" is typically practiced for iron and folic acid.

Enrichment of food staples differs from the other types of nutrition-intervention programs (fortification of branded foods, dietary diversification or modification, and supplementation) in a number of ways. One important difference is that it does not require a behavioral change or any deliberate action by the recipients in order to be effective. It is also thought to be the most cost-effective method of delivering deficient nutrients to a wide population group. One constraint is that viable enrichment programs require that the cereal be centrally processed in sizable mills with a capacity of over 20 metric tons per day.

It should be recognized that establishing a national cereal enrichment or fortification program is extremely

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difficult, so progress in this area will be slow at best. The main impetus for having such programs is to supply more iron, since iron-deficiency anemia and related problems are currently more widely recognized than nutritional problems due to zinc. Also, diets that lead to iron-deficiency anemia tend to also provide inadequate zinc, and inhibitors of iron absorption also inhibit absorption of zinc. Therefore, it would make good sense to include zinc along with iron in fortification programs for countries exhibiting problems of iron deficiency. Areas of the world that have the highest risk of these deficiencies include parts of Africa, Iran, Egypt, and the Indian subcontinent. In these areas, it is recommended to strongly consider inclusion of zinc with any iron enrichment or fortification program.

Some major questions related to including zinc in a cereal-enrichment program need to be addressed: When should zinc be included in a cereal fortification or enrichment program? What source of zinc should be used? What level of zinc should be added? How much will it cost? What effects, if any, will it have on product quality and acceptability?

Types of zinc salts

The question of which zinc source to add is usually determined by a combination of economics, effect on food quality, and bioavailability. The different zinc compounds that might be used are shown in table 1.

The zinc compound used should meet the purity requirements of the Food Chemicals Codex (FCC) and, ideally, have GRAS (Generally Recognized as Safe) status. It is interesting that although a number of studies have been carried out with zinc acetate, it is not GRAS and therefore cannot be used in food fortification in the United States. Zinc acetate is reported to have an offensive taste when not diluted with sugar and a high reactivity in foods. For these reasons, zinc acetate has not been used in commercial food fortification, and this lack of use has prevented it from receiving GRAS status.

Unlike the iron sources used in cereal enrichment, all of the zinc sources are white, so inherent color is not a problem or a reason for choosing between the different sources. A potential problem is that some of the more soluble sources cause color changes in certain food ingredients, such as chocolate. Also, some zinc salts may impart undesirable flavors. For example, zinc oxide has a bitter taste, and zinc sulfate is very astringent. It does not appear that these inherent tastes carry over to the fortified foods, but very little testing has been done on this. Zinc acetate has a slight odor of acetic acid, whereas the other salts are odorless. As with ferrous sulfate, there is both a dried and a hydrated form of zinc sulfate. The dried form is preferred over the hydrated form because the latter form is reported to cause problems with caking.

Perhaps the most important difference between the zinc sources is their solubility, since it relates to both bioavailability and effects on food quality. Zinc oxide is insoluble in water but soluble in dilute acid. This implies that it will be inert in dry foods but that it should be available for absorption after exposure to stomach acid. Zinc acetate, zinc gluconate, and zinc sulfate are soluble in water, and zinc chloride is very soluble.

Zinc oxide is the most commonly used zinc source for the fortification of cereal-based foods, followed by zinc sulfate and, to a very limited extent, zinc gluconate. Zinc sulfate is specified for use in the corn-soy blend [1] and the wheat-soy blend produced for the US Food for Peace Program. It is also used in similar weaning or complementary foods made throughout the world. Zinc acetate and zinc gluconate find use in dietary supplements and some weaning foods.

There is a wide range in the cost, as shown by the cost per unit weight of zinc in table 1. The least expensive source is zinc oxide, which costs approximately one-third as much as zinc sulfate, the next cheapest source. These cost differences are more important in general fortification programs for food staples such as wheat flour, salt, and sugar, where profit margins are slim, than they are in the more profitable, branded

TABLE 1. Properties of different zinc compounds

Zn compound	GRAS[a] status	Solubility	% Zn	Cost (US$/kg)	Cost (US$/kg Zn)
Acetate	No	Soluble in water	29	5.60	19.30
Chloride	Yes	Very soluble in water	48	20.74	43.20
Gluconate	Yes	Soluble in water	14	5.00	35.70
Oxide	Yes	Not soluble in water. Soluble in dilute acids and alkali	80	2.33	2.90
Stearate	Yes	Insoluble	10		High
Sulfate, dried	Yes	Soluble in water	36	3.74	10.40
Sulfate, hydrated	Yes	Soluble in water	23	3.15	13.70

a. GRAS: Generally Recognized as Safe by the US Food and Drug Administration.

foods, such as breakfast cereals or dietary supplements. Based on these costs and current fortification practices, zinc oxide and zinc sulfate would be the primary candidates to consider in cereal-enrichment programs.

Bioavailability and effect on product quality of different zinc salts

The bioavailability of different zinc salts has been nicely reviewed by Davidsson [2]. Most of the studies were done with supplements, which showed an advantage of the soluble forms over the insoluble ones. There have been very few studies on zinc absorption from fortified cereals. One study on rats by Ranhotra et al. [3] at the American Institute of Baking showed little difference in absorption of the different sources when they were added to bread. Absorption of zinc carbonate was poor, but absorption of zinc oxide was nearly as good as that of the more soluble forms. Ranhotra et al. also found no adverse effects on bread quality. In a chick feeding study [4] with a corn and soybean meal, the bioavailability of two commercial forms of zinc sulfate was 99% and 81%, whereas that of two sources of zinc oxide was 78% and 54%. A second experiment found a bioavailability of 94% for zinc sulfate and 74% for zinc oxide. Studies in Turkey [5] reported that bread fortified with zinc acetate had an acceptable quality and was effective in preventing zinc deficiency in children. It appears that zinc fortification has little detrimental effect on flour and bread quality. One study, in which levels up to 500 ppm of zinc were added as zinc chloride, even showed a beneficial effect of this addition on baking [6].

The differences in the availability of zinc from different compounds are largely a function of their solubility, which is dependent on pH, both in the food and in the stomach. One study [7] compared the absorption of zinc from zinc acetate and zinc oxide in humans with so-called low (≤ pH 3) and high (≥ pH 5) gastric pH. Absorption was higher from the acetate than from the oxide in subjects with high gastric pH (low gastric acid production), but the absorption was similar when gastric acid production was normal. Absorption of both forms of zinc was greater at low gastric pH than at high gastric pH. These results suggest that although the oxide may have sufficient bioavailability for a normal population, it might not be suitable for malnourished children whose stomach pH is higher because of reduced ability to produce stomach acid, and that therefore it should not be used in therapeutic supplementation programs.

Most of the past work on bioavailability has been done with supplements or with zinc salts added to cooked food. The actual chemical form of the zinc after different types of food processing is not known. Further research is required to address the effect of processing, particularly fermentation and baking, on the chemical form of zinc fortificants and how it might affect bioavailability.

Levels of zinc to add to cereals and effect on dietary intakes

Traditionally, the levels of micronutrients added to cereals are based on restoring the levels in refined cereals back to the level contained in the whole grain product. Table 2 shows the levels of zinc in the three main cereal staples before and after milling. The addition of 20 ppm zinc to white wheat flour would nearly replace the zinc lost to milling.

Higher levels of zinc might be added to obtain a greater benefit, particularly when the intake of the cereal is not high. Higher zinc addition rates are often used in the special complementary foods and in branded ready-to-eat cereals. For example, 40 ppm zinc is added to the corn-soy blend and 50 ppm to the World Food Program’s version of the corn-soy blend [9].

Even at the lower levels of 20 to 30 ppm of added zinc, the impact on meeting dietary requirements would be significant. At a reasonable daily intake of 100 g of cereal enriched with 20 ppm zinc, children would receive 20% of their daily zinc requirement. Such fortification levels would not present a safety hazard. At the likely upper limit of a sustained intake of 500 g of cereal per day, which would supply over 1800 kcal/day of energy, the maximum amount of zinc added to the diet would be 15 mg/day, or 100% of the adult recommended daily intake, if all cereals were fortified with 30 ppm zinc.

Zinc in current and proposed cereal-fortification programs

As mentioned, the addition of 20 ppm zinc would restore the zinc level of white flour back to the level contained in whole wheat. This is the level selected for use in Mexico. A higher enrichment level of 30 ppm zinc has been proposed for wheat flour in Indonesia and other Far East countries, where consumption is lower. In these cases, the zinc would be added along with B vitamins and iron.

TABLE 2. Natural levels of zinc in cereals (ppm) before and after milling

Product	Wheat	Maize	Rice
Whole grain	29	18	20
Milled	7	7	11

Based on data from ref. 8.

In Mexico the ingredient cost of adding 20 ppm zinc, using zinc oxide as specified by the Mexican government, would amount to US$0.09 per metric ton (MT) of enriched flour, which is about 9% of the total ingredient cost for all fortificants of US$1.05/MT. If zinc sulfate was used, the ingredient cost of zinc would be US$0.32/MT, or about 25% of the total cost of all fortificants. The ingredient cost of adding 30 ppm zinc in the proposed Indonesian programs comes to US$0.16/MT with the oxide, or US$0.57/MT with the sulfate. Zinc oxide would account for 14% of the total ingredient cost of fortificants, whereas zinc sulfate would account for 43% of the total cost. The ingredient cost is the major expense in cereal enrichment. Labor, quality control, and equipment costs are far less and do not change whether or not zinc is included.

The cost of zinc fortification with the oxide is close to the cost of iron fortification according to the WHO/UNICEF scheme of adding 30 ppm iron of ferrous sulfate or 60 ppm of reduced iron. Using zinc sulfate, however, makes zinc fortification more expensive than iron fortification. In either case, the ingredient cost for including zinc is quite reasonable, considering that the total ingredient cost for most programs is increased by no more than 15% if the oxide is used. Inclusion of zinc in a cereal-enrichment program should be economically feasible for many countries.

One problem in encouraging developing countries to include zinc with any iron-fortification program is the lack of a precedent for doing so in the developed countries. Zinc is not part of the US cereal-enrichment standards, nor is it likely to be included, even though this was proposed in the National Academy of Sciences 1974 recommendations for changing the US enrichment program [10]. One possibility that should be explored is to include zinc in the fortification of processed cereal foods provided as food aid under the United States P.L. 480 Food for Peace Program. These foods are wheat flour, corn meal, and bulgur, none of which is currently enriched with zinc [9]. Enrichment of these foods with zinc would not cost much and would help demonstrate the utility and feasibility of adding zinc to cereal food staples.

As long as zinc is always added along with iron, millers and regulators can use the quality control tests developed for iron enrichment to help ensure that the flour has been properly enriched. There is a simple, semiquantitative iron spot test that millers use to test whether a premix has been added. The atomic absorption spectrophotometric method used in the quantitative determination of iron in enriched cereals can also measure zinc with little modification. Normally, mills run only the iron spot test as a routine quality control procedure. The quantitative testing is done occasionally by outside laboratories and by regulatory agencies.

There is certainly a lot more happening in zinc fortification of cereal food staples now than there was a few years back. We are woefully lacking in some good application and bioavailability research, which is needed to both promote zinc enrichment and determine which sources to use. Areas where research is needed include product quality and sensory testing, including the effects of added zinc sulfate and oxide on wheat flour, bread, masa flour, tortilla, and rice; and availability testing, including the absorption of zinc oxide from nonfermented wheat flour products (e.g., pasta and noodles), the absorption of added zinc in high-phytic-acid products (e.g., chappatis and whole corn ugali), and the absorption of added zinc from tortillas.

References

1. USDA. Commodity Specifications. Announcement CSB9, Purchase of corn-soy blend for use in export programs. Kansas City, Mo, USA: Kansas City Commodity Office, 1998.
2. Davidsson L. Zinc. In: Hurrell R, ed. The mineral fortification of foods. London: Leatherhead International, 1999:54–83.
3. Ranhotra GS, Loew RJ, Puyat LV. Bioavailability and functionality (breadmaking) of zinc in various organic and inorganic sources. Cereal Chem 1977;54:496–502.
4. Sandoval M, Henry PR, Ammerman CB, Miles RD, Littell RC. Relative bioavailability of supplemental inorganic zinc sources for chicks. J Anim Sci 1997;75:3195–205.
5. Saldamli I, Koksel H, Ozboy O, Ozalp I, Kilic I. Zinc-supplemented bread and its utilization in zinc deficiency. Cereal Chem 1996;73:424–7.
6. Vadlamani KR, Seib PA. Effect of zinc and aluminum ions in breadmaking. Cereal Chem 1999;76:355–60.
7. Henderson LM, Brewer GJ, Dressman JB, Swidan SZ, DuRoss DJ, Adair CH, Barnett JL, Berardi RR. Effect of intragastric pH on the absorption of oral zinc acetate and zinc oxide in young healthy volunteers. J Parenter Enteral Nutr 1995;19:393–7.
8. Drake DL, Gebhardt SE, Matthews RH. Composition of foods: cereal grains and pasta. Washington, DC: USDA Nutrition Monitoring Division, Human Nutrition Information Service, 1989.
9. Ranum P. Final report of the micronutrient assessment project. Washington, DC: SUSTAIN, 1999.
10. National Academy of Sciences. Proposed fortification policy for cereal-grain products. Report LCCC 74–10542. Washington, DC: National Academy of Sciences, 1974.

Nutrition, health, and economic development: Some policy priorities

Alok Bhargava

Abstract

Most developing countries face different resource and infrastructural constraints that limit their economic growth. Nutritional deficiencies, poor environmental conditions, and inadequate educational infrastructure hamper children's learning, which is critical for the future supply of skilled labor and hence for economic development. There is a need to assign priorities for resource allocation among nutritional, health-care, and educational policies. This paper draws implications from several studies using data from less developed countries within a multidisciplinary framework. It concludes that iron supplementation of pregnant women and access to family-planning services are likely to enhance maternal and infant health. Where iodine deficiency is endemic, iodized salt is important for preventing cognitive damage to the fetus. Higher intakes of protein and micronutrients such as iron are important for children's physical growth, morbidity, and learning. Improved sanitation and vaccines against infections will prevent loss of vital nutrients. Investments in educational infrastructure, including adult literacy programs, are beneficial for children's cognitive development. Nutrition and health policies based on long-term considerations will lead to a well-trained labor force enabling non-resource-rich developing countries to escape from poverty traps.

Introduction

Many people in less-developed countries are undernourished. Although some population groups face shortages of staple foods, such as cereals, that are necessary for meeting energy needs, the quality of diets remains poor for a majority of the people. Typically, a poor-quality diet supplies inadequate quantities of protein and micronutrients such as iron that are essential for various human functions [1]. Where the environment is poor in iodine, consumption of iodated salt by pregnant women is important for the normal development of the fetal brain. Furthermore, low intakes of fresh fruits and vegetables during certain seasons cause vitamin A, vitamin C, and other nutrient deficiencies, making individuals more susceptible to disease. Adequate intakes of such nutrients are essential for maintaining adult health and productivity over the life span; children's development critically depends on the quality of diet that the household can afford.

Nutrients such as protein and iron are typically found in high concentration in animal products, which are relatively expensive and often beyond the budgets of the poorest households. Because of poor sanitation and unhygienic environments, infectious diseases often deplete the body's stores of vital nutrients such as iron [2]. Many studies in developing countries have shown that poor nutritional status is associated with reduced productivity [3–5]; even the walking pace of individuals can be affected by iron-deficiency anemia [6].

The link between poor adult health status and child development has not, however, been explored sufficiently in the literature. For example, parents in poor health may be forced to leave household tasks to children. Such tasks reduce the amount of time children spend on school-related activities and learning. Because learning is a cumulative process, children with excessive household responsibilities are likely to complete fewer years of education. The future supply of skilled labor is therefore likely to be affected by poor parental health. Because skilled labor is critical for economic growth, it is important to formulate comprehensive policies to protect children's cognitive development. The purpose of this comment is to draw policy implications from research modeling health and nutrition data from less-developed countries within a multidisciplinary framework.

It is important to recognize that there is considerable variation in food intake among individuals within a country. This is especially true for the intake of meat and other energy-dense foods whose consumption has risen with household incomes. For example, in

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countries such as India and China, prevalence rates have increased for chronic conditions such as obesity, diabetes, hypertension, and cardiovascular diseases [7]. Thus, health policies now have to tackle not only the traditional diseases of poverty but also chronic conditions caused by excessive food consumption and a sedentary lifestyle. Because the latter diseases afflict primarily the well-off groups who are likely to be better educated, a preventive approach via educational messages and counseling is appealing. By contrast, public health policies are necessary to improve the health status and productivity of undernourished people.

The importance of an educated labor force for economic development has been recognized in the economics literature. Studies using data at the country level from emerging economies such as those in East Asia have reported positive associations between human capital and economic growth [8]. However, it is essential to understand the pathways through which educational levels are achieved by populations in different settings. A detailed knowledge of the interrelationships between nutrition, infection, and child development would be useful for allocation of resources. Thus, for example, undernourished children are unlikely to fully benefit from the resources spent on the educational infrastructure.

Although nutritionists and psychologists have emphasized the link between children's nutritional status and cognitive development [9], the studies have typically observed a small number of children over a short time span. Because school dropout rates are high in many developing countries, without a mobilization of resources for enhancing children's learning, a large number of children are likely to remain functionally illiterate. For creating a well-trained labor force, therefore, it is essential to look at stages in children's development and identify factors that can be influenced by public policies in a cost-effective way.

Maternal and infant health

To understand the causes underlying children's poor nutritional status and cognitive development, it is useful to begin with the effects of poor maternal nutritional status on intrauterine growth. In a research setting, it is often difficult to relate the effects of food intake during pregnancy to birth outcomes, partly because of the expense of continuously measuring food intake. When food-intake data were available at some time points, insignificant associations were reported in Kenya between nutrient intake by pregnant women during the trimesters and birth outcome [10]. However, the prepregnancy nutritional status, represented by the maternal body mass index, was a significant predictor of infant birth weight, length, and head circumference. Although maternal hemoglobin concentration was not significantly associated with anthropometric measurements at birth, it was a significant predictor of growth in head circumference and weight between the ages of one and six months.

Hemoglobin concentration is a good indicator of iron-deficiency anemia. Moreover, iron body stores are typically low in undernourished women and may be inadequate to support full fetal growth. Thus, iron stores depleted by each pregnancy cannot be replenished in a short time interval because of poor diet quality, helminth infections, etc. These issues have not been fully integrated in demographic research. For example, using data from household demographic surveys, researchers have found that short birth intervals are associated with increased child mortality [11]. This can be explained by the fact that retarded babies are at a greater risk of mortality.

In the absence of family-planning methods for birth spacing, infants born to undernourished women are more likely to be physically retarded and hence susceptible to infections; mothers with many children also have less time for child care. Further, poor physical development of the surviving infants can restrict brain growth, thereby hindering cognitive development. It is evident that there is considerable biological and socioeconomic information underlying the reported negative associations between birth intervals and child mortality. Policies affecting such factors would ultimately determine the future supply of skilled labor that is critical for economic growth.

The interrelationships between poor diet quality, access to family planning, birth outcomes, and child development have not been thoroughly investigated in the literature. This is because an elaborate longitudinal study would require observing children for extended periods and would be expensive. However, these interrelationships determine the sequence of events underlying the formation of a skilled labor force. The relative importance of the nutritional, demographic, and economic factors will depend on the level of economic and social development in a country.

For example, some economists have emphasized the link between female education and decline in fertility, while asserting that family-planning methods are unlikely to be effective [12]. The analysis was based on national averages of fertility rates that cannot capture the differential access to family-planning and healthcare services for the well-off and poor households in developing countries. Moreover, there is a large unmet demand for family-planning services even among so-called backward population groups in countries such as India that is also likely to affect the health of the surviving children [13]. Ignoring such factors can lead to misleading conclusions, such as poor efficacy of family-planning programs for maternal and child health.

Further, iron-deficiency anemia is widely prevalent, especially among pregnant women in developing countries such as Bangladesh [14]. Iron supplementation of anemic women is relatively inexpensive, costing approximately US$2.50 per woman per year [15] and can improve birth outcomes [1]. Having a large number of children has severe consequences to an undernourished woman. For example, girls may be assigned a disproportionate number of household tasks that interfere with education. It is important that poor couples have access to contraceptives for birth spacing. Interventions that include both the provision of birthcontrol measures and iron supplements are likely to achieve better maternal and infant outcomes. Healthier infants have a greater potential for learning.

Preschool children

In developing countries, a large majority of the infants who survive until one year of age can expect to reach old age [16]. For the surviving children, the early childhood period is critical for brain development. Because protein and iron are important for brain growth [17], maintaining a steady supply of these nutrients is a challenge to policy makers. Shortfalls in micronutrient intakes can reduce physical growth and exacerbate sickness, thereby reducing activity levels. Food-supplementation programs, for example, such as the provision of a nutritious high-protein beverage supplement for Guatemalan children 6 to 24 months of age, have brought lasting improvement in growth and cognitive performance [18]. Moreover, using data on Kenyan and Egyptian children, psychologists have found associations between the intake of particular nutrients and the scores on cognitive tests [19, 20].

Learning is a complex process that is influenced by the stimulation received at home. For example, the time that Kenyan mothers spent talking with infants in the period between one and six months of age was a significant predictor of the infants' scores on eight items from the Bayley Infant Behavior Record given at six months [10]. Iron-deficiency anemia is associated with lower scores on cognitive tests of school-aged children [9, 21, 22], including adolescent girls [23, 24], as well as of infants and preschool children [25, 26].

The logistics of running large-scale food-supplementation programs for preschool children in developing countries are formidable, although such programs are often necessary for certain population groups. National policies often give priority to children's sicknesses. Vaccinations against preventable diseases can not only enhance child survival but also enhance children's nutritional status, as can environmental sanitation and personal hygiene that reduces diarrheal disease. The helminth infections widely prevalent in developing countries reduce nutrient absorption, and some increase iron loss [27, 28]. These infections are easy to prevent.

There is a paucity of studies that can inform policy decisions based on cost-benefit considerations for reducing iron-deficiency anemia among children. For example, it is known that increasing the intake of bioavailable iron can improve iron status, and some parasitic infections deplete iron stores. Yet there are few studies comparing the efficacy and costs of increasing bioavailable iron intake and treatment of helminth infections. Most interventions against helminth infections have been short-term approaches [29], and reinfection rates remain high. Vaccines against various types of helminth infection, such as hookworm, that are under development [30] would be useful for preventing iron loss. A vaccine against malaria would improve children's survival chances and health status in endemic areas.

Improved sanitation can also achieve lower rates of enteric infection due to bacteria, viruses, and helminths. Although treatment of sewage is often beyond the budgets of local governments, better methods for waste disposal can reduce disease transmission and improve the quality of drinking water, thereby reducing nutrient loss through enteric diseases. In the absence of detailed studies that include nutritional, environmental, and population variables in a developing country, it is more difficult to design and implement cost-effective strategies for enhancing the health status of preschool children. Nevertheless, children's nutritional intakes must be above a certain threshold to enable them to fully benefit from school education. Data on nutrient intakes have become available from many developing countries; hemoglobin concentration is now measured in many household surveys. Such nutritional information is useful for targeting the most vulnerable children who are likely to face the worst environmental conditions as well.

School-aged children

In addition to nutrient deficiencies and disease transmission due to poor environmental conditions, policy makers have to address the role played by the educational infrastructure in the cognitive development of school-aged children. Broadly speaking, children's learning in school is affected by three sets of factors. First, regular school attendance is essential for learning. Second, the school environment should be stimulating; teachers should be qualified for their job, and books and school supplies should be adequate. Third, children need additional time at home to master the concepts introduced in school. For example, in the analysis of data from the Embu region of Kenya [22], the time spent by children in school and their parents' scores on cognitive tests were positively associated with the children's scores on various components of cognitive tests. Children's illnesses were negatively associated with the scores. Although some of the factors affecting the scores can be easily influenced, cognitive development of children requires long-term strategies, because physical and intellectual development are intertwined with levels of nutrition [31, 32].

Children's school attendance plays an important role in learning. Repeated sicknesses can hinder school attendance. Although a number of school-based interventions have assessed the effects of anthelmintic treatment on the scores on cognitive tests, no study has attempted to quantify the effects of such treatment on the duration and intensity of illnesses [33]. Moreover, children from poor households are likely to be performing household tasks that reduce the time available for studying at home. Poor parental health can exacerbate the situation. Meager teaching materials and poorly trained teachers may not be sufficient to sustain children's interest in learning. Children who cannot keep up with school examinations usually discontinue school. Because learning is a cumulative process, such children seldom return to school.

It is evident that creating an educated labor force in many poor countries is likely to be a long-term goal requiring several decades to achieve. Nevertheless, high literacy rates have been achieved in some poor societies, such as in the Indian state of Kerala [34]. Moreover, with the media now reaching remote areas in developing countries, parental aspirations for the well-being of their offspring are rising. Couples want to have fewer children so that they can be educated to take advantage of the new opportunities. Greater availability and utilization of family-planning and health-care services, achieved through national and international efforts in populous countries, is likely to result in fewer children born at longer time intervals. Birth spacing enables poor couples to stretch their meager resources and would facilitate children's escape from poverty via education.

Conclusions

Many factors promote economic development, among which population health is of critical importance. Countries need to devise different strategies for increasing prosperity, depending on their level of economic and social development [35]. For example, resource-rich countries, such as those in the Middle East, have enhanced the nutritional status of their citizens through better food intake and access to health care.

Some countries in East Asia have prospered without natural resources by reducing family size and educating children to create a well-trained labor force. However, the developmental problems in many countries in Africa and Asia remain complex and cannot be viewed in terms of simple paradigms. Rather, policy makers need to devise specific policies for each country, taking into account the nutritional and health status of their populations, the environmental conditions, and the educational infrastructure. In populous African countries, the AIDS epidemic is reducing the life expectancy of both unskilled and skilled population groups and is hindering economic development. Without better policies, many of the poor countries are unlikely to escape from the poverty trap in the foreseeable future.

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References

1. UNICEF/UNU/WHO/MI. Preventing iron deficiency in women and children. Technical consensus on key issues. Boston, Mass, USA: International Nutrition Foundation, 1999.
2. Scrimshaw NS, Taylor CE, Gordon JE. Interactions of nutrition and infection. Am J Med Sci 1959;237:367–403.
3. Basta SS, Soekirman MS, Karyadi D, Scrimshaw NS. Iron deficiency anemia and the productivity of adult males in Indonesia, Am J Clin Nutr 1979;32:916–25.
4. Spurr GB. Nutritional status and physical work capacity. Yearbook Phys Anthropol 1983;26:1–35.
5. Bhargava A. Nutritional status and the allocation of time in Rwandese households. J Econometrics 1997; 77:277–95.
6. Bhargava A, Reeds PJ. Requirements for what? Is the measurement of energy expenditure a sufficient estimate of energy needs? J Nutr 1995;125:1358–62.
7. Paeratakul S, Popkin BM, Keyou G, Adair L, Stevens J. Changes in diet and physical activity affect the body mass index of Chinese adults. Int J Obesity 1998; 22:424–31.
8. Kim JI, Lau LJ. The sources of economic growth in the East Asian newly industrialized countries. J Jpn Int Econ 1994;8:235–71.

9. Scrimshaw NS. Malnutrition, brain development, learning and behavior. Nutr Res 1998;18:351–79.
10. Bhargava A. Modeling the effects of maternal nutritional status and socioeconomic variables on the anthropometric and psychological indicators of Kenyan infants from age 0–6 months. Am J Phys Anthropol 2000;110:89–104.
11. Cleland J, Sathar ZA. The effect of birth spacing on childhood mortality in Pakistan. Pop Stud 1984;38:401–18.
12. Pritchett LH. Desired fertility and the impact of population policies. Pop Dev Rev 1994;20:1–55.
13. Bhargava A. Family planning, gender differences and infant mortality: evidence from Uttar Pradesh, India. J Econometrics (in press).
14. Bhargava A, Bouis H, Scrimshaw NS. Dietary intakes and socioeconomic factors are associated with the hemoglobin concentration of Bangladeshi women. J Nutr (in press).
15. Levin H, Pollitt E, Galloway R, McGuire J. Micronutrient deficiency disorders. In: Jamison D, Mosley W, Measham A, Bobadila J, eds. Disease priority in developing countries. Oxford, UK: Oxford University Press, 1993:421–54.
16. World Bank. World development indicators on cd rom. Washington, DC: World Bank, 1998.
17. Monckeberg F. Effects of malnutrition on physical growth and brain development. In: Prescott JW, Read MS, Coursin D, eds. Brain function and malnutrition: neurophysiological method of assessment. New York: John Wiley, 1975:15–52.
18. Pollitt E, Gorman KS, Engle PL, Martorell R, Rivera J. Early supplementary feeding and cognition. Monograph of Society for Research in Child Development 1993;58(7):1–99.
19. Sigman M, Neumann C, Jansen AAJ, Bwibo N. Cognitive abilities of Kenyan children in relation to nutrition, family characteristics, and education. Child Dev 1989;60:1463–74.
20. Wachs TD, Bishry Z, Moussa W, Yunis F, McCabe G, Harrison G, Sweifi E, Kirksey A, Galal O, Jerome N, Shaheen F. Nutritional intake and context as predictors of cognition and adaptive behavior of Egyptian school-age children. Int J Behav Dev 1995;18:425–50.
21. Pollitt E. Iron deficiency and cognitive function. Annu Rev Nutr 1993;13:521–37.
22. Bhargava A. A dynamic model for the cognitive development of Kenyan school children. J Educ Psychol 1998;90:162–6.
23. Brunner AB, Joffee A, Duggan AK, Casella JF, Brandt J. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficiency adolescent girls. Lancet 1996;348:992–6.
24. Ortega RM, Gonzalez-Fernandez M, Paz L, Andrés P, Jiménez LM, Jiménez MJ, Gonzalez-Gross M, Requejo AM, Gaspar MJ. Influencia del status en hierro en la atencion y rendimiento intelectual de un collectivo de adolescentes Espanoles. Arch Latinoam Nutr 1993;43:6–11.
25. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. N Engl J Med 1991;352:687–95.
26. Soewondo S, Husaini M, Pollitt E. Effects of iron deficiency on attention and learning processes in preschool children: Bandung, Indonesia. Am J Clin Nutr 1980;50(suppl):667–74.
27. Barness LA. Nutrition and nutritional disorders. In: Behrman RE, Kliegman RM, Nelson WE, Vaughan VC, eds. Nelson's textbook of pediatrics. 14th ed. Philadelphia: W.B. Saunders, 1992:105–46.
28. Awasthi S, Pande VK. Prevalence of malnutrition and intestinal parasites in preschool slum children in Lucknow. Indian Pediatr 1997;34:599–605.
29. Dickson R, Awasthi S, Williamson P, Demellweek C, Garner P. Effects of treatment for intestinal helminth infection on growth and cognitive performance in children: systematic review of randomized trials. BMJ 2000;320:1697–1701.
30. Hotez P, Ghosh K, Hawdon JM, Narasimhan S, Jones B, Shuhua X, Sen L, Bin Z, Haechou X, Hainan R, Heng W, Koski RA. Experimental approaches to the development of a recombinant hookworm vaccine. Immunol Rev 1999;171:163–72.
31. Scrimshaw NS. Nutrition and health from womb to tomb. Nutr Today 1996;31:55–67.
32. Bhargava A. Modelling the effects of nutritional and socioeconomic factors on the growth and morbidity of Kenyan school children. Am J Hum Biol 1999;11:317–26.
33. Bhargava A. Conclusions should have been based on broader considerations. Letter to the Editor. BMJ 2000;321:1225.
34. International Institute for Population Sciences. National Family Health Survey. Mumbai, India: International Institute for Population Sciences, 1995.
35. Bhargava A, Jamison DT, Lau LJ, Murray CJL. Modeling the effects of health on economic growth. J Health Econ (in press).

Community-based study of obesity among children and adults in Riyadh, Saudi Arabia

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Abstract

Nowadays obesity is a major public health problem. It is a main risk factor for many fatal diseases. Our study aimed to determine the prevalence of obesity among children and adults in Riyadh and to investigate the associated sociodemographic factors. A cross-sectional, population-based sample of Riyadh was selected through the two-stage cluster sampling technique. All participants attended the local primary health-care center, and a questionnaire interview to obtain sociodemographic data was completed for each. Anthropometric measurements of weight and height were performed. Body mass index (BMI) was calculated, and children having a BMI ≥ 95th age- and sex-specific percentile and adults with a BMI ≥ 30 were considered obese. There were 4,775 participants: 1,848 children and 2,927 adults. Among the children, 10.5% were overweight and 8.7% were obese. Among the adults, 32.4% were overweight and 21% were obese. Among children, a multivariate logistic regression analysis showed that age 6 to 10 years (odds ratio, 2.21; 95% confidence interval, 1.4–3.5) and non-Saudi nationality (odds ratio, 2.2; 95% confidence interval, 1.31–3.7) were associated with childhood obesity. Among adults, urban residence (odds ratio, 1.5; 95% confidence interval, 1.23–1.83), female sex (odds ratio, 2.03; 95% confidence interval, 1.64–2.53), and marriage (odds ratio, 2.11; 95% confidence interval, 1.57–2.82) were associated with obesity in adults, as was Saudi nationality and age above 30 years. Obesity is an important public health problem in Riyadh.

Introduction

Obesity is a severe public health problem. It is a major determinant of many noncommunicable diseases, including type 2 diabetes mellitus, coronary heart disease, stroke, cancer, gallbladder diseases, musculoskeletal disorders, and respiratory problems [1, 2]. Obesity is a very expensive disease that causes a great loss of quality of life and suffering, not only to the patients but also to the families [3, 4]. It is a leading cause of pediatric hypertension [5] and a known risk factor for adult obesity [6, 7]. Obese persons, particularly children and adolescents, often suffer from a lowered self-esteem that affects their school performance and their peer relationship, leading to long-term psychological effects [8–10]. In some communities obese persons may also suffer from social stigmatization and discrimination [11].

Saudi Arabia has gone through a significant economic development over the last decades [12]. Western lifestyle with respect to nutritional habits has replaced the traditional ones and, coupled with improvement in health services, has resulted in the emergence of noncommunicable diseases, including obesity [13, 14].

Not many studies have focused on obesity at the community level in Saudi Arabia. Some were conducted among adults [15–17] and a few among children, but not in the same regions [18]. The aim of the present work was to determine the prevalence of overweight and obesity among both children and adults in Riyadh, Saudi Arabia, and to investigate the associated sociodemographic factors.

Materials and methods

Subjects and measurements

The study was conducted using a cross-sectional approach. An institutional review board approved the study, and oral informed consent was obtained. A sample size of 1,014 was calculated on the assumption of a 12% prevalence of obesity, an error of 0.05, and a degree of precision of 0.02. The sample size was increased more than fourfold to adjust for the design effect of cluster sampling. A two-stage cluster sampling

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technique was used to recruit the participants. Thirty clusters were selected, covering all geographic areas of Riyadh. Each cluster consisted of inhabitants of 15 households selected randomly from the cluster area.

Selected subjects were requested to attend the local primary health-care center, and all agreed to participate. A questionnaire to obtain sociodemographic data, such as age, sex, marital status, and level of education, was completed for each subject at the center. The subjects were weighed on a lever balance while wearing light clothes. Height was measured by using the vertical upright bar of the balance. Weight was recorded to the nearest 0.01 kg and height to the nearest 0.01 m.

The body mass index (BMI), defined as the weight in kilograms divided by the square of the height in meters, was calculated. For assessing obesity in adults, the recommendations of the 1997 World Health Organization (WHO) consultation on obesity were used: normal, BMI < 25 kg/m^2; overweight or preobese, 25–29.9 kg/m^2; class I obesity, 30–34.9 kg/m^2; class II obesity, 35–39.9 kg/m^2; and class III obesity, ≥ 40 kg/m^2 [1]. Overweight among children is defined as BMI ≥ 85th age- and sex-specific percentile, and obesity as BMI ≥ 95th age- and sex-specific percentile values of the American National Health and Nutrition Examination Survey (NHANES) [6, 19, 20].

Statistical analysis

SPSS software was used for analysis. BMI was summarized as means and standard deviations. The prevalences of overweight and obesity were calculated as percentages. Crude association between sociodemographic variables and body weight status was tested by the chi-square test at 95% level of significance. Multiple logistic regression analysis was used to assess the strength of association of each variable with overweight and obesity after adjustment for other confounders.

Results

There were 4,775 participants in the study, of whom 1,848 were children 6 to 17 years of age and 2,927 were adults over age 17. Table 1 shows that 10.5% of the children were overweight and 8.7% were obese. Among adults, 32.4% were overweight and 21% were obese. Females had higher rates of overweight and obesity than males both as children (11.9% vs 9.1% and 9.7% vs 7.7%, respectively) and as adults (31.6% vs 31.2% and 25.6% vs. 15.1%, respectively). The association between sex and body weight status was statistically significant ($p < .05$).

The highest prevalence of overweight and obesity was among children 6 to 10 years old (12.3% and 11.8%, respectively) (table 2). Children in the rural area were more likely to be overweight or obese (11.2% and 10.1%, respectively) than urban children (10% and 7.7%, respectively). However, the association between body weight status and area was not statistically significant ($p < .05$). Children with below intermediate education had the highest prevalences of overweight and obesity (10.7% and 9.2%, respectively). Age and nationality were significantly associated with body weight status.

There was an independent significant association between obesity and non-Saudi nationality (odds ratio, 2.2; 95% confidence interval, 1.31–3.7) and the age group from 6 to 10 years (odds ratio, 2.21; 95% confidence interval, 1.4–3.5) (table 3). On the other hand the association between obesity and female sex was not significant (odds ratio, 1.28; 95% confidence interval, 0.92–1.78).

Adults in their fifth decade had the highest prevalence of obesity (33.7%), and those 18 to 29 years old had the lowest prevalence (10.6%) (table 4). Both overweight and obesity were higher in urban than in rural areas (32.5% vs 29.4% and 23.7% vs 16.8%, respectively). Overweight and obesity were higher among married people than single people (35.4%

TABLE 1. Body weight status among children and adults in Riyadh, Saudi Arabia, 1999

	Males		Females		Total	
Subjects and status	No.	%	No.	%	No.	%
Children (6–17 yr)						
Normal	782	83.2	712	78.4	1,494	80.8
Overweight	86	9.1	108	11.9	194	10.5
Obese	72	7.7	88	9.7	160	8.7
Adults (> 17 yr)						
Normal	700	53.7	693	42.7	1,393	47.6
Overweight	407	31.2	513	31.6	920	32.4
Class I obesity	160	12.3	261	16.1	421	14.4
Class II obesity	28	2.1	115	7.1	143	4.9
Class III obesity	9	0.7	41	2.4	50	1.7

TABLE 2. Sociodemographic characteristics and body weight status among children (6–17 years) in Riyadh, Saudi Arabia, 1999

Characteristic	Normal	Overweight	Obese	p
	No. (%)			
Age (yr)				
6–10	548 (75.9)	89 (12.3)	85 (11.8)	<.01
10–13	549 (83.1)	63 (9.5)	49 (7.4)	
14–17	289 (85.5)	30 (8.9)	19 (5.6)	
Area				
Urban	917 (82.2)	112 (10.0)	86 (7.7)	0.13
Rural	577 (78.7)	82 (11.2)	74 (10.1)	
Nationality				
Saudi	1,221 (70.3)	175 (10.1)	140 (8.1)	<.01
Non-Saudi	73 (65.2)	19 (17.0)	20 (17.9)	
Education				
Below intermediate	1,163 (80.1)	156 (10.7)	133 (9.2)	0.2
Intermediate	283 (83.5)	30 (08.8)	26 (7.7)	
Secondary	48 (84.2)	8 (14.0)	1 (1.8)	

TABLE 3. Results of multivariate logistic regression analysis for sociodemographic characteristics and obesity among children (6–17 years) in Riyadh, Saudi Arabia, 1999

Characteristic	OR	95% CI
Female	1.28	0.92–1.78
Non-Saudi	2.2[a]	1.31–3.7
Age (yr)		
6–10	2.21[a]	1.40–3.5
11–17	1.37	0.84–2.24

OR, Odds ratio; CI, confidence interval
a. $p < .05$.

vs 19.3% and 25.1 vs 8.9%, respectively). University graduates had the highest rate of overweight (36.9%), followed by those who were illiterate (33.1%), but obesity was higher among the illiterate (26.2%) than among university graduates (21.4%). The association between age, area, nationality, marital status, and body weight status was statistically significant.

Table 5 shows that urban residence (odds ratio, 1.5; 95% confidence interval, 1.23–1.83), female sex (odds ratio, 2.03; 95% confidence interval, 1.64–2.53), and marriage (odds ratio, 2.11; 95% confidence interval, 1.57–2.82) independently had a significant association with obesity. All age groups over 30 years also had a significant association with obesity ($p < .05$).

Discussion

Obesity is second only to cigarette smoking among modifiable risk factors for morbidity and mortality [21]. The prevalence of obesity in adults is 10% to 25% in most countries of western Europe and 20% to 25% in some countries of the Americas [1]. Our work found that around one-third (31.6%) of adults in Riyadh were overweight and more than one-fifth (21%) were obese. This finding is consistent with results of other studies in Saudi Arabia [15, 17, 22]. Higher rates were reported among those attending primary health-care centers [23, 24], but this may be an indicator that obese persons use health services more than persons with ideal body weights, who are usually in better health.

There is an increasing prevalence of childhood obesity and its concomitant health risks [25]. The present study showed that 10.5% of children were overweight and 8.7% were obese. These figures are lower than those among schoolchildren in the kingdom [18]. The difference may be attributed to the use of a different definition of obesity. Internationally the reported prevalence of overweight among children in Europe was 4.9% to 14.3%. In the United States, the prevalence of childhood overweight increased from 7.6% between 1973 and 1980 to 10.9% between 1988 and 1991, and the results of the 1994 National Health and Nutrition Examination Survey III suggested that the prevalence continued to increase [26].

The high prevalence of obesity in Riyadh reflects the profound changes in society and behavioral patterns of the community over the last 20 to 30 years [1]. Genetic factors may be involved because of the high rate of mating between obese persons and because of consanguineous marriage [27]. Some authors have reported that among Saudis obesity is equated with health and wealth and is therefore valued [28].

Children aged 6 to 10 years had the highest prevalence of childhood overweight and obesity (12.3% and 11.8%, respectively). This may be due to inadequate school physical-activity programs for these children. Among adults, the prevalence of obesity peaked during

TABLE 4. Sociodemographic characteristics and body weight status among adults (> 17 years) in Riyadh, Saudi Arabia, 1999

Characteristic	Normal	Overweight	Obese	p
	No. (%)			
Age, yr				
18–29	655 (66.4)	227 (23.0)	105 (10.6)	<.01
30–39	297 (38.6)	287 (37.3)	186 (24.2)	
40–49	144 (29.6)	179 (36.7)	164 (33.7)	
50–59	97 (31.3)	123 (39.7)	90 (29.0)	
≥ 60	204 (54.7)	100 (26.8)	69 (18.5)	
Area				
Urban	774 (43.8)	575 (32.5)	420 (23.7)	<.01
Rural	623 (53.8)	341 (29.4)	194 (16.8)	
Nationality				
Saudi	1237 (48.4)	776 (30.4)	542 (21.2)	0.02
Non-Saudi	160 (43.0)	140 (37.6)	72 (19.4)	
Marital status				
Single	539 (71.8)	145 (19.3)	67 (8.9)	<.01
Married	858 (39.4)	771 (35.4)	547 (25.1)	
Education				
Illiterate	558 (40.6)	455 (33.1)	360 (26.2)	<.01
Primary	322 (47.9)	222 (33.0)	128 (19.0)	
Intermediate	236 (61.9)	99 (26.0)	46 (12.1)	
Secondary	211 (63.4)	78 (23.4)	44 (13.2)	
University	70 (41.7)	62 (36.9)	36 (21.4)	

the fifth decade (33.7%). This finding is consistent with results of national epidemiological household surveys among adults conducted in 1993 [17]. In Bahrain the prevalence of obesity was higher among those who were 50 years old or more [29].

The present work shows that overweight and obesity were more common among females than males in both children and adults. The results of national and international studies agree with this finding [12, 15, 17, 22, 30, 31]. Many factors may contribute to the high prevalence of obesity among females, including hormonal influences [32] and a cultural attitude of restricting physical activity by women [17]. Furthermore, the majority of housewives in the study were multiparous and had housemaids to help them with most of the physical work at home.

Marriage increases the prevalence of obesity [29]. We found that 25.1% of married people were obese, as compared with only 8.9% of single people. This finding was supported by a study in Al-Khobar [33]. Marriage may increase obesity through changes in lifestyle and diet.

Illiterate adults had the highest prevalence of obesity. The same finding was observed in the national survey [16]. In a study in Spain, illiteracy not only had a positive relationship with obesity but proved to be the sole variable associated with it [34]. There was a higher prevalence of obesity among urban than among rural residents (23.7% vs 16.8%). This has also been observed by others [16, 35].

TABLE 5. Results of multivariate logistic regression analysis for sociodemographic characteristics and obesity (body mass index ≥ 30) among adults in Riyadh, Saudi Arabia, 1999

Characteristic	OR	95% CI
Urban areas	1.5[a]	1.23–1.83
Female	2.03[a]	1.64–2.53
Saudi	1.03	0.76–1.39
Married	2.11[a]	1.57–2.82
Education		
Illiterate	1.23	0.84–1.78
Primary	1.11	0.75–1.63
Intermediate	0.97	0.61–1.53
University	1.55	0.93–2.58
Age (yr)		
30–39	3.51[a]	2.59–4.74
40–49	1.87[a]	1.31–2.66
50–59	2.03[a]	1.54–2.69
≥ 60	3.05[a]	2.15–4.32

OR, Odds ratio; CI, confidence interval
a. $p < .05$.

Overweight and obesity constitute a severe public health problem among children and adults in Riyadh. The highest prevalences of obesity were associated with 6 to 10 year old children and adults over age 30, Saudi nationality, female sex, urban area, and marriage in adults.

Recommendations

We recommend early development of national programs for the prevention and control of obesity, including school nutritional educational programs; promotion of a healthful lifestyle, including more physical activity; and replacement of the traditional Saudi diet with a diet lower in energy density, particularly among females.

References

1. World Health Organization. Obesity epidemic puts millions at risk from related diseases. WHO/46. Geneva: WHO, 1997.
2. Hill JO, Melanson EL. Overview of the determinants of overweight and obesity: current evidence and research issues. Med Sci Sports Exerc 1999;31(suppl 11): S515–21.
3. Kurscheid T, Lauterbach K. The cost implications of obesity for health care and society. Int J Obes Relat Metab Disord 1998;22(suppl 1):S3–5.
4. Levy E, Levy P, Le Pen C, Basdevant A. The economic cost of obesity: French situation. Int J Obes Relat Metab Disord 1995;19:788–92.
5. Melnik TA, Rhoades SJ, Wales KR, Cowell CQ, Wolfe WS. Overweight school children in New York City: prevalence estimates and characteristics. Int J Obes Relat Metab Disord 1998;22:7–13.
6. Rios M, Fluiters E, Perez Medez LF, Garcia-Mayor EG, Garcia-Mayer RV. Prevalence of childhood overweight in Northeastern Spain: a comparative study of two periods with a ten year interval. Int J Obes Relat Metab Disord 1999;23:1095–8.
7. Kromeyer-Hauschild K, Zellner K, Jaeger U, Hoyer H. Prevalence of overweight and obesity among school children in Jena (Germany). Int J Obes Relat Metab Disord 1999;23:1143–50.
8. Tershakovec AM, Weller SC, Gallagher PR. Obesity, performance and behaviour of black urban elementary children. Int J Obes Relat Metab Disord 1994; 8:323–7.
9. Hill AJ, Draper E, Stack J. A weight on children's minds: body shape dissatisfaction at 9 years old. Int J Obes Relat Metab Disord 1994;18:383–9.
10. Garn SM, La Velle M. Two decade follow up of fatness in early childhood. Am J Dis Child 1985;139:181–5.
11. Khaodhier L, McCowen KC, Blackburn GL. Obesity and its comorbid conditions. Clin Cornerstone 1999; 2(3):17–31.
12. Al-Nuaim AR. High prevalence of metabolic risk factors of cardiovascular diseases among Saudi population aged 30–64 years. Int J Cardiol 1997;62:227–35.
13. Al-Balla SR, Bamgboye EA, Sekait M, Balla M. Causes of morbidity in the elderly population of Saudi Arabia. J Trop Med Hyg 1993;96:57–62.
14. Al-Balla SR, Bamgboye EA, Sekait M, Al-Rasheed R. Pattern of adults admission into medical wards of King Khalid University Hospital, Riyadh (1985–1990). Saudi Med J 1993;13:8–13.
15. Al-Rehaimi AA, Bjorntrop P. Obesity and fat distribution in women from Saudi Arabia. Int J Obes Relat Metab Disord 1992;16:1017–9.
16. Al-Niaim AR, Al-Mazroa Y, Al-Rubeaan K, Al-Attas O, Khoja T, Al-Daghari N. National chronic metabolic diseases survey. Riyadh: Ministry of Health 1997;Part II:135–41.
17. Al-Nuaim AA, Bamgboye EJ, Al-Rubeaan KA, Al-Mazrou Y. Overweight and obesity in Saudi Arabian adult population: role of sociodemographic variables. J Commun Health 1997;22:211–23.
18. Al-Nuaim AR, Bamgboye EA, Al-Herbish A. The pattern of growth and obesity in Saudi Arabian male school children. Int J Obes Relat Metab Disord 1996;20:1000–5.
19. Poskitt E. Defining childhood obesity: the relative body mass index. Acta Paediatr 1995;84:961–3.
20. Must A, Dallal GE, Dietz WH. Reference data for obesity: 85th and 95th percentiles of body mass index (wt/ht^2) and triceps skinfold thickness. Am J Clin Nutr 1991;53:839–46.
21. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, Hennekens CH, Speizer FE. Body weight and mortality among women. N Engl J Med 1995;333:677–85.
22. Al-Mahross F, Al-Roomi K. Overweight and obesity in the Arabian Peninsula: an overview. J R Soc Health 1999;119:251–3.
23. Al-Shammari SA, Khoja TA, Al-Subaie AS. Transcultural attitude towards being overweight in patients attending health centers, Riyadh, Saudi Arabia. Fam Pract Res J 1994;14(2):149–56.
24. Al-Shammari SA, Khoja TA, Al-Maatouq MA. The prevalence of obesity among Saudi males in the Riyadh region. Ann Saudi Med 1996;16:269–73.
25. Al-Attas OS, Laajam MA, Khan MS, Al-Drees AZ. Obesity and major metabolic indices in newly diagnosed Saudi diabetic patients. Trop Geogr Med 1990;42:40–5.
26. Centers for Disease Control (CDC). Update: prevalence of overweight among children, adolescents and adults-United States, 1988–1994. JAMA 1997;277:1111.
27. Hebebrand J, Wulftange H, Goerg T, Ziegler A, Hinney A, Barth N, Mayer H, Remschmidt H. Epidemic obesity: Are genetic factors involved via increased rates of assortative mating? Int J Obes Relat Metab Disord 2000;3:345–53.
28. Al-Subaie A. Psychiatry in Saudi Arabia: cultural perspectives. Transcult Psychiat Res Rev 1989;26:245–62.
29. Al-Mannai A, Dickerson JW, Morgan JB, Khalfan H. Obesity in Bahraini adults. J R Soc Health 1996; 116:30–40.
30. Rasheed P, Abou-Hozaifa BM, Khan A. Obesity among young Saudi female adults: a prevalence study on medical and nursing students. Public Health 1994;108:289–94.
31. Kordy MN, El-Gamal FM. A study of pattern of body mass index (BMI) and prevalence of obesity in a Saudi population. Asia Pacific J Public Health 1995;8:59–65.
32. Newcombe RG. Development of obesity in parous women. J Epidemiol Commun Health 1982;36:306–9.

33. Rasheed P. Perception of body weight and self reported eating and exercise behaviour among obese and non obese women in Saudi Arabia. Public Health 1998; 2:409–14.
34. Gutierrez-Fisac JL, Rodriguez Artalejo F, Gualler-Castillon P, Banegas Banegas JR, del Rey Calero J. Determinants of geographical variations in body mass index (BMI) and obesity in Spain. Int J Obes Relat Metab Disord 1999;23:342–7.
35. Soyannwo MA, Kurashi NY, Gadallah M, Hams J, El-Essawi O, Khan NA, Singh RG, Alamri A, Beyari TH. Body mass index (BMI) in the Saudi population of Gassim. Afr J Med Sci 1998;27:117–21.

Local food price analysis by linear programming: A new approach to assess the economic value of fortified food supplements

André Briend, Elaine Ferguson, and Nicole Darmon

Abstract

Linear programming can be applied to identify a nutritionally adequate diet of the lowest cost, since price and nutrient contents are linearly related to food weight. Most computer spreadsheets now include an easy-to-use solver function that is suitable for this purpose. This approach can also be used to estimate the effect of introducing a food supplement on the minimal cost required to provide a nutritionally adequate diet. It can also provide an estimate of the expenses saved by families in relation to the sums spent by the donor after the distribution of a food supplement. This method is illustrated by comparing the economic value of two food supplements, a traditional blended flour and a nutrient-dense spread (a "foodlet") in rural Chad. The limitations of this approach and the need to interpret its findings carefully in relation to field observations are discussed.

Introduction

Food fortification is often advocated on the grounds that it is an inexpensive strategy to increase the nutritional value of the diet of the poorest populations. Even if the cost of food fortification is low, its implementation requires a strong commitment from local governments, food industries, and donor agencies, who do not always perceive the benefits of this approach. In part, this is because the benefits of food fortification are not easily quantified in economic terms.

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Linear programming analysis is a powerful approach for identifying a low-cost nutritionally adequate diet [1], but it has been only infrequently used for this purpose in human nutrition [2–4]. This paper also illustrates how this technique can be used to estimate the economic benefits expected from the introduction of different fortified foods using local food prices. As an example, it will compare the economic value of a classical blended food with that of a nutrient-dense spread known as a "foodlet," a highly fortified food that can be regarded as a big tablet (foodlet for food + tablet) [5], for childhood diets in Chad.

Estimation of the minimum price of a balanced ration by linear programming

Linear programming is a technique that minimizes a linear function of a set of variables while respecting multiple linear constraints on these variables. It can therefore be used to minimize the price of a diet while fulfilling constraints introduced to ensure a palatable, nutritionally adequate diet. The linear function to be minimized in this case is the cost of a balanced diet, as expressed mathematically below:

$$\text{Cost of ration} = W_1C_1 + W_2C_2 \ldots + W_nC_n$$

where C_1, C_2, C_n are the costs per unit weight of foods 1 to n.

The various constraints needed to ensure a palatable, nutritionally adequate diet include nutritional constraints on the minimum energy and nutrient content in the diet, as well as food-consumption constraints on the maximum acceptable daily portions of individual foods. These constraints should be expressed as linear constraints to facilitate the analysis, and are briefly described below.

An adequate diet can be defined as a diet fulfilling all current nutritional recommendations, with each nutrient being present in amounts equal to or superior to its recommended daily allowance (RDA). In mathematical terms, this can be expressed by a set of inequalities:

$$N_{11} W_1 + N_{12} W_2 \ldots + N_{1n} W_n > \text{RDA } N_1$$
$$\cdots\cdots\cdots$$
$$N_{j1} W_1 + N_{j2} W_2 \ldots + N_{jn} W_n > \text{RDA } N_j$$

where

- n is the number of foods habitually consumed by the local population;
- j is the number of nutrients for which an RDA is specified;
- $W_1, W_2 \ldots W_n$ are the weights of foods 1 to n; and
- $N_{11}, N_{12}, \ldots N_{jn}$ are the contents of nutrients 1 to j per unit of weight of food 1 to n.

All these constraints are linear constraints, because they consist of a simple sum of products. If the RDA selected for iron and zinc assumes moderate bioavailability, then an additional constraint is required on the phytate:zinc molar ratio (PZ), whereby the PZ is below 15. This constraint is not linear, because it is based on a ratio. However, it can be expressed as a linear constraint by transforming it to

$$15\,Z - P > 0$$

where Z and P are the molar zinc and phytate contents of the diet.

This equation can also be transformed into a sum of products in the following form:

$$(15Z_1 - P_1)\bullet W_1 + (15Z_2 - P_2)\bullet W_2 \ldots + (15Z_n - P_n)\bullet W_n > 0$$

where Z_n and P_n represent the molar zinc and phytate contents of food n.

If used with only nutritional constraints, linear programming can lead to unrealistic diets, since this approach will select a few low-cost, highly nutritious foods, such as beans, green leafy vegetables, dry fish, or liver, which will not be eaten in large quantities in practice. To avoid this problem, constraints on maximum daily portion sizes for each food should be introduced. Ideally these portion sizes should be defined by using food-consumption survey data collected from the population of interest or, if this is not possible, from a similar community.

Linear programming is based on a mathematical iterative approach involving multiple calculations of products and sums, which can be quickly performed by a personal computer. Calculations presented below were done with the Excel 97 (Microsoft) spreadsheet, which has a linear programming function called a "solver function" in all its recent versions. This function is found in the "tools" menu. For some versions of this program, this function is not automatically installed. However, it can be imported from the original CD of the program. It is also important to note that the options assuming that all constraints are linear and that all variables are positive should be activated before starting the analysis.

The solver function of recent spreadsheet versions also accepts nonlinear constraints in the model. Hence, constraints based on complex mathematical functions can be introduced, giving, for example, a better approximation of the mineral availability than the phytate/zinc ratio. Nonlinear programming, however, is a more complex technique and may in some cases give nonoptimal solutions, unless the analysis is repeated several times using different initial values for food variables. Therefore, only linear programming is recommended, at least in the initial stages of an analysis.

An example based on a food price survey in Chad

To illustrate the merits of linear programming for identifying low-cost diets, the minimum price of a nutritionally adequate ration for a child aged three to six years was estimated from a price survey performed in Mao, Chad. Mao is the main city of Kanem Province in a semi-desert part of northern Chad. Only a limited number of foods traditionally given to children in this area were included in the analysis.

For this analysis, local food prices were converted into prices in US$ per kilogram of the edible portion. The nutritional constraints used in the analysis were based on the preliminary World Health Organization (WHO) nutritional recommendations for children of this age group [6] for all nutrients except calcium. For calcium, the UK recommendation [7](450 mg/day) was used instead, because an optimized diet was not realizable with the use of the preliminary WHO recommendations for calcium (600 mg/day). An additional constraint was also introduced on the PZ (i.e., < 15) to warrant the assumption of moderate zinc and iron availability [8]. These constraints are presented in table 1.

To ensure that optimized diets were realistic, food constraints were also introduced that limited the daily portions of available foods (see table 2). Food-consumption data were not available for three- to six-year-old children in Chad, and therefore the 75th centiles of observed intakes of three- to six-year-old rural Malawian children were used instead, assuming that limits of intake in these two poor rural communities would be similar. These data were collected by using three-day weighed food records in the postharvest season in rural Malawi [9]. Some adjustments were also made to take into account local food availability in Mao. For example, the 75th centile for fresh fish intake in Malawi was used to define the food constraint for fresh meat intake in Chad. *Spirulina*, a green-blue alga growing spontaneously in the oasis in this part of Chad and traditionally collected and dried to prepare a nutrient-rich sauce, was also added to the food database. During the optimization process, the nutritional contents of all foods except *Spirulina* [10] were taken from the World food dietary assessment system (version 2.0) [11].

TABLE 1. Nutritional constraints introduced in the models for estimating the minimal price of a balanced ration for three- to six-year-old children in Mao, Chad

Nutrient	Amount
Macronutrients [6]	
Energy	> 1550 kcal
Proteins	> 20 g
Minerals	
Calcium	> 450 mg [7]
Magnesium	> 76 mg [6]
Zinc	> 4.8 mg [6]
Iron	> 5 mg [6]
Phytate/zinc	< 15 mg [(8]
Vitamins [6]	
Vitamin B1	> 0.6 mg
Vitamin B2	> 0.6 mg
Vitamin B6	> 0.6 mg
Niacin	> 8 mg
Folate	> 200 µg
Vitamin B12	> 1.2 µg
Vitamin C	> 30 mg
Vitamin A	> 450 µg RE

The diet obtained by cost minimization with local foods is shown in first column of table 2. Most foods present in the food database were selected, and several, such as sweet potatoes, eggs, and dried fish, were set at the maximum allowed. By definition, this diet fulfils all nutritional constraints, which means that its nutrient content is equal to or above the RDA for all nutrients. This diet should not be regarded as an ideal diet, but as the lowest-cost nutritionally adequate diet for this population where dietary quality is limited by cost.

The most difficult nutritional constraints to fulfill in this setting were energy, niacin, folate, and PZ, which were at the minimum and maximum levels for the constraints imposed (table 3). This optimized diet should be regarded as a first estimate, and it must be followed by field observations to confirm that the optimized diet is compatible with general food-consumption patterns of children in the region. Additional constraints can also be added if necessary: for example, constraints on the percentage of energy provided by different food groups to delimitate local food-consumption patterns. Conversely, some constraints may be relaxed, such as the upper limit on daily portions for highly acceptable foods. As a rule, tightening constraints will increase the estimated minimum price of a balanced ration, whereas relaxing them will lower this price.

TABLE 2. Food consumption constraints imposed during optimization, and daily portions of foods selected for an optimized (low-cost, nutritionally adequate) diet for a three- to six-year-old child, with and without introduction of traditional blended flour and highly nutrient-dense spread in the linear programming model

Food	Maximum amount of food allowed during diet optimization (g)	Amount of food selected (g)[a]		
		Only local foods	Flour added[b]	Spread added[c]
Spirulina alga	5	**5**	0	0
Groundnuts	45	0	0	0
Banana	75	**75**	0	0
Maize flour	255	0	53	**255**
Millet flour	175	71	23	0
Dried okra	65	33	0	0
Oil	17	**17**	**17**	**17**
Cowpeas	60	16	6	3
Eggs	40	**40**	0	0
Onions	4	**4**	0	0?
Sweet potatoes	165	**165**	156	6
Dried fish	25	**25**	**25**	12
Rice	110	**110**	110	39
Mutton	80	**80**	0	36
Nutrient-dense spread	40	NA	NA	26
Blended flour	255	NA	120	NA
Cost (US$)		0.704	0.329	0.286

a. Foods set at their maximum level by linear programming are in boldface type. Amounts are given for foods as bought from the market, before preparation. NA, not allowed.
b. Estimated cost: US$1/kg.
c. Estimated cost: US$3/kg.

This example has been presented to demonstrate how linear programming can be used to delineate the minimal cost required to provide a nutritionally adequate diet for a population of three- to six-year-old children in this part of rural Chad. Such information is useful for nutrition education purposes and for evaluating economic factors in relation to dietary adequacy.

Comparison of the economic impact of two possible food aid programs in Chad

In some communities, an affordable, nutritionally adequate diet based on local foods may be difficult to achieve without the introduction of a low-cost fortified-food supplement. In these circumstances, linear programming analysis can be used to evaluate the effect of alternative food supplements on the price of a ration. To illustrate this application of linear programming, we have compared the economic value of two food supplements, a traditional blended flour and a highly nutrient-dense spread, defined as a "foodlet" [12]. Their nutritional values are shown in table 4. For nutrient-dense spread, the fortification levels chosen were those previously field-tested in Algeria [13]. High fortification levels are made possible in this spread by the attractive taste of peanut, which can easily hide high levels of unpalatable vitamins and minerals. The flour was a blend of maize and cowpea flours with sugar, fortified with a standard mineral and vitamin mix [14]. This formula of this blend is similar to that of the blended flour produced and distributed in food-supplementation programs in Chad in recent years.

To estimate the maximum amount of blended flour a child of this age can reasonably eat per day, the 75th centile of intake for maize flour in Malawi was chosen [9]. For nutrient-dense spread, it was limited to 40 g, which was the average intake observed in the supplementation study in Algeria on children aged three to five years.

In this example, it was assumed that blended flour and nutrient-dense spread could be produced in N'Djamena, the capital city of Chad, and transported to Mao at a cost of US$1 and US$3 per kilogram, respectively. These figures—although realistic—are used only to illustrate the use of linear programming and should not be taken literally. The production costs for nutrient-dense spread were estimated from the price of locally available ingredients and the cost of adding a mineral and vitamin mix.

Table 2 shows the optimized ration and minimal costs obtained when blended flour and nutrient-dense spread were added to the list of foods available for selection in the ration, using the same constraints as those previously described (see tables 1 and 2). As outlined above, these rations must be interpreted carefully and ideally should be field-tested for their acceptability and, if necessary, reanalyzed using additional constraints.

To illustrate the use of linear programming for defining the economic impact of fortified supplements, we will assume that the proposed diets (table 2) were acceptable and palatable. This analysis showed that the inclusion of either blended flour or nutrient-dense spread in the model decreased the estimated minimum

TABLE 3. Nutritional content of diets for a three- to six-year-old child selected by linear programming analysis[a]

Nutrient	Only local foods	Flour added	Spread added
Macronutrients			
Energy (kcal)	**1,550**	**1,550**	**1,550**
Protein (g)	60	49	40
Minerals (mg)			
Calcium	546	617	**450**
Magnesium	179	215	388
Zinc	7	11	20
Iron	13	20	16
Phytate/zinc < 15 mg	**15**	**15**	14
Vitamins			
Vitamin B1 (mg)	0.63	0.92	1.88
Vitamin B2 (mg)	0.81	1.01	1.53
Vitamin B6 (mg)	1.3	1.2	1.7
Niacin (mg)	8	14	23
Folate (μg)	**200**	293	**200**
Vitamin B12 (μg)	1.3	1.2	1.2
Vitamin C (mg)	39	64	**30**
Vitamin A (μg RE)	1,850	2,130	526

a. Nutrients set at their allowed limit by the program are in bold type.

TABLE 4. Nutritional composition of traditional blended flour and highly nutrient-dense spread (per 100 g)

Nutrient	Flour	Spread
Energy (kcal)	330	630
Protein (g)	12	10
Minerals (mg)		
Calcium	126	1000
Magnesium	58	156
Iron	12	42
Zinc	6	41
Phytates	544	289
Vitamins		
Vitamin A (μg RE)	400	2000
Vitamin C (mg)	30	125
Vitamin B1 (mg)	0.4	3.5
Vitamin B2 (mg)	0.5	4
Vitamin B6 (mg)	0.2	3.5
Vitamin B12 (μg)	1	3.5
Folic acid (μg)	200	500
Niacin (mg)	6.8	50

price of a balanced ration (table 2), using quantities less than the maximum limit specified in the program. Assuming that these foods are distributed freely (food aid), the resultant savings for a nutritionally adequate diet per child per family will be equal to the difference between the total cost of the diet without and with the supplement (both costs shown in table 2) plus the price of the supplement itself. In this example, this saving (D in table 5) is slightly higher for blended flour than for nutrient-dense spread. In contrast, the ratio between the amount saved by the families and the amount spent by the donors (R in table 5) is higher for nutrient-dense spread than blended flour, because of the higher cost of blended flour (B in table 5).

The latter gives a better comparative estimate of the economic value of the alternative food supplements evaluated (i.e., each US$1 spent by the donor on nutrient-dense spread saved US$7.07 for the families, as compared with US$4.15 for blended flour). In other words, in this example, the foodlet would be more cost-effective than the traditional blended food. These results were not easily predictable when the costs were compared in isolation (i.e., the prices per kilogram and per quantity of energy), a result emphasizing the merits of this type of analysis.

This analysis will also show when a proposed program has a ratio of amount saved to amount spent less than 1, which means that the money saved by the families will be below the amount spent by the donor. This is likely to be the case for unfortified blended flour prepared from locally available foods: these foods are more expensive than the sum of the basic ingredients used in their composition and have no superior nutritional value compared with the meal a mother would prepare at home with the same ingredients.

Limitations of the presented approach and possible future applications

Linear programming is a very powerful tool for analyzing the cost of a nutritionally adequate ration prepared from different locally available foods. Only the general principles and selected applications of the approach have been presented here. It is noteworthy that this method could be further refined by taking into account costs not included in this example, such as the cost of targeting food distribution, of administrative overheads, or of training food aid staff. It could also take into account foods grown by the family by giving them an economic value.

The sensitivity of linear programming to selected constraints, however, is its major weakness. Clearly, this approach should not be used in isolation, and the validity of its conclusions should be field-tested. The chosen set of nutritional constraints should be based on internationally accepted nutritional recommendations, such as those published by international organizations. Ideally, the food-consumption constraints used in the model should be derived from food-consumption data collected in the community of interest. In their absence, constraints based upon survey data collected in a comparable environment, as presented in this example, may be a useful starting point for the analysis. Building up an international database of food-consumption constraints for different age groups, especially for nutrient-dense foods, would facilitate the application of this method. The validity of these constraints could then be confirmed and if necessary adjusted on the basis of a series of simple observations in the community itself.

This method has wide applications for different types of nutrition-intervention programs, including supplementation, fortification, and agriculture programs. Despite its limitations, it clearly provides useful information for evaluating the economic benefits of different intervention programs for the poor.

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TABLE 5. Estimation of the economic impact and efficacy of blended flour and highly nutrient-dense spread

Food	Minimum cost of ration for child with fortified supplement (A) (from table 2) (US$)	Cost of supplement (B) (price per kilogram amount in table 2)(US$)	Estimated cost for family of ration for child when food supplement is given C = (A–B)(US$)	Estimated saving for family to feed child balanced diet when supplement is given D = (MEP[a] – C)(US$)	Ratio of amount saved by family to amount spent by donor (R = D/B)
Flour	0.33	0.12	0.21	0.50	4.2
Spread	0.29	0.07	0.22	0.49	7.1

a. MEP, Minimum estimated price for a nutritionally adequate diet for a three- to six-year-old child from local foods: US$0.70.

References

1. Smith VE. Linear programming models for the determination of palatable human diets. J Farm Econ 1959; 31:272–83.
2. Foytik J. Very low-cost nutritious diet plans designed by linear programming. J Nutr Educ 1981;13:63–6.
3. Henson S. Linear Programming analysis of constraints upon human diets. J Agric Econ 1991;42:380–93.
4. Briend A, Darmon N. Determining limiting nutrients by linear programming: a new approach to predict insufficient intakes from complementary foods. Pediatrics 2000;106:1288–9.
5. Gross, R. Micronutrient supplementation throughout the lifecycle. Rio de Janeiro: Ministry of Health and UNICEF, 1999.
6. FAO/WHO. Preliminary report on recommended nutrient intakes. Joint FAO/WHO expert consultation on human vitamin and mineral requirements. Bangkok: FAO, 1998. http://www.fao.org/WAICENT/FAOINFO/ECONOMIC/ESN/vitrni.pdf
7. Department of Health and Social Security. Dietary reference values for food energy and nutrients for the United Kingdom. Report of the panel on dietary reference values of the committee on medical aspects of food policy. Rep Health Soc Subj (Lond) 1991;41:1–210.
8. WHO/FAO/IAEA. Trace elements in human nutrition and health. Geneva: World Health Organization, 1996.
9. Ferguson EL, Gibson RS, Opare OC, Ounpuu S, Thompson LU, Lehrfeld J. The zinc nutriture of preschool children living in two African countries. J Nutr 1993;123:1487–96.
10. Falquet, J. Spiruline. Aspects nutritionnels. Geneva: Antenna Technologie, 1996.
11. Calloway DH, Murphy SP. WorldFood dietary assessment system. (Version 2), computer program. Berkeley, Calif, USA: University of California,1998. http://otl.berkeley.edu/Worldfood.html
12. Briend A. Highly nutrient-dense spreads: a new approach to delivering multiple micronutrients to high-risk groups. Br J Nutr 2001;85(suppl 2):S1–S5.
13. Branca F, Lopriore C, Guidoum Y, Briend A, Golden M. Multi-micronutrient fortified food reverses growth failure and anaemia in 2–5 year-old stunted refugee children. Scand J Nutr 1999;43:51S (abstract).
14. Anonymous. Enhancing the nutritional quality of relief diets. Proceedings of the workshop on enhancing the nutritional quality of relief diets held in Washington, DC, 28–30 April 1999. Washington DC: USAID. 1999. http://www.foodaid.org/enhance.htm

Breastfeeding and weaning practices of mothers and infants in Uzbekistan

Gulnara Semenova

Editorial introduction

This study of infant-feeding practices sponsored by UNICEF in 1994 and 1995 was the first of its kind in Uzbekistan. It extends and confirms the findings of a similar investigation in 1994 by Wellstart in Kazakhstan. Both studies used primarily qualitative interview and observation techniques to obtain information in depth from mothers and health providers. The approach is an adaptation of the rapid assessment procedures (RAP) derived from anthropological methodologies [1]. The author of this Uzbekistan study, Dr. Gulnara Semenova, received special training in qualitative field study methods at the University of Connecticut through an International Nutrition Foundation fellowship funded by UNICEF.

Her observations and conclusions are supported by transcribed quotations from mothers and health workers selected from the many obtained to illustrate the various problems and issues identified. In order to preserve the flavor of the original observations, the quotations have been largely left as translated by the author, and no attempt has been made to put them in idiomatic English. All social and health scientists interested in breastfeeding behavior will find this a fascinating and valuable work.

Her study confirms that nearly all mothers in Uzbekistan successfully breastfeed their infants for at least four to six months and most for much longer. Contrary to local medical beliefs, the mothers are not undernourished. Weight gain during pregnancy and the birthweights of their infants were in the normal range. Concurrently a quantitative survey of the dietary intakes of these same mothers and their infants using two random 24-hour dietary recalls was conducted by Dr. Shamil Tajibaev, Associate Director of the Institute of Nutrition, in cooperation with Dr. Gulnara Semenova. The detailed and quantitative findings will be reported elsewhere.

Despite finding a high rate of early breastfeeding, Dr. Semenova's study reveals a series of practices that make it more difficult for mothers to initiate and maintain breastfeeding adequately. These include separation of the mother and child for hours or even one or two days at birth, "prelacteal" feeding of infants, and lack of prenatal instruction in breastfeeding management. In addition, the rigid day feeding schedule required in the hospital, with no night feedings, and the lack of access of the mother to the child for breastfeeding on demand, decreed by former Soviet Union policy, are serious obstacles. Most serious in its ultimate consequences, however, is the large number of mainly subjective indicators used by doctors to determine that a mother should not breastfeed her infant. As pointed out in the article, almost none of these are consistent with World Health Organization (WHO) recommendations or with currently accepted medical practices.

Commercial infant formulas are rarely used, but there is an urgent need to adopt the International Code of Marketing of Breast Milk Substitutes [2] to protect mothers from more aggressive promotion of these substitutes, as the country becomes increasingly open to both national and multinational products and marketing of these formulas. There is also a need to control the marketing and promotion of "follow-up formula" that may not technically violate the Code but that can be promoted in ways that discourage prolonged breastfeeding.

The adequate weight gain of mothers during pregnancy and the normal birthweights of their infants indicate that protein-energy malnutrition is not a significant issue for this population. However, a serious problem of iron-deficiency anemia was encountered in both mothers and infants [Tajibaev S, personal communication, 1996]. From 40% to 60% of mothers and infants suffer from anemia, nearly all of it due to iron deficiency. This was confirmed by data from a subsequent DHS survey in Uzbekistan [3] that found a 56% prevalence rate of anemia among a large representative sample of Uzbek

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women, 11% of which was moderate to severe. Given the lasting functional consequences for cognitive performance of iron-deficiency anemia in infancy and its debilitating effects on mothers, this constitutes a health emergency. For both ethical and economic development reasons comprehensive programs for the control of iron-deficiency anemia and the promotion and facilitation of breastfeeding deserve high priorities.

Nevin S. Scrimshaw
Editor

References

1. Scrimshaw SCM, Hurtado E. Rapid assessment procedures for nutrition and primary health care Anthropological approaches to improving programme effectiveness. French, English, Spanish. Los Angeles: UCLA Latin American Center, 1997.
2. WHO. International code of marketing breast-milk substitutes. Geneva: World Health Organization, 1981.
3. Macro International. Uzbekistan demographic and health survey 1996. Tashkent, Usbekistan: Institute of Obstetrics and Gynecology and Ministry of Health, and Calverton, Md, USA: Macro International, 1997.

Abstract

Qualitative data on infant-feeding practices were collected in four urban and four suburban sites in Uzbekistan. The qualitative interviews combined with observation were conducted with 209 women at their households and with 118 health professionals at health-care facilities. Despite finding a high rate of early breastfeeding, the study revealed a series of practices that make it more difficult for mothers to initiate and maintain breastfeeding adequately. These include separation of the mother and child at birth, "prelacteal" feeding of infants, and lack of prenatal instruction in breastfeeding management. In addition, the rigid day feeding schedule required in the hospital, with no night feedings, and the lack of access of the mother to the child for breastfeeding on demand, decreed by former Soviet Union policy, were serious obstacles. Most serious in its ultimate consequences, however, was the large number of mainly subjective indicators used by doctors to conclude that a mother should not breastfeed her infant. Almost none of these were consistent with WHO recommendations or with currently accepted medical practices. Despite these obstacles, nearly all mothers in Uzbekistan successfully breastfeed their infants for at least four to six months and most for much longer. Contrary to local medical beliefs, the mothers are not undernourished. Weight gain during pregnancy and the birthweights of their infants were in the normal range.

Introduction

During the period from 11 March to 10 May 1995, in eight sites of Uzbekistan, the fieldwork of a qualitative study on "Breastfeeding and Weaning Practices in Uzbekistan" was conducted as a joint project of the Kazakhstan Institute of Nutrition (KIN) of the National Academy of Sciences (NAS) of Kazakhstan, the International Nutrition Foundation (INF), and the United Nations Children's Fund Area Office for the Central Asian Republics and Kazakhstan (UNICEF CARK AO). During the fieldwork, four urban and four suburban sites were visited. Qualitative interviews were conducted with 209 women by four local interviewers supervised by the author, who also visited the households. At each location there were also visits to maternity hospitals, "women's consultation sites," and children's polyclinics. The author interviewed 118 health professionals.

The qualitative study was based on semistructured, detailed interviews. The mothers were interviewed in their homes; obstetricians and midwives were interviewed in maternity hospitals and the women's consultation sites. Interviews with pediatricians, neonatologists, and nurses were held in maternity hospitals, children's polyclinics, and the neonatal units of children's hospitals. During interviews the researchers observed actual breastfeeding and weaning practices in order to cross-check their observations with the descriptions provided by mothers and health professionals.

Positive perceptions of breastfeeding

Breastfeeding is considered a natural method of infant feeding in Uzbekistan. Uzbek women do not need encouragement to breastfeed. They do it willingly, and most choose it as their only method of infant feeding. "What else can you give to the baby except breast?" they say. "It is natural—it is given by God."

Almost 90% of the mothers in the study samples breastfed their children. "If the child is breastfed with love, you will have milk, and the child will be healthy and will love you and will feed you in old age." Investigators heard many variations of this saying around the country. "If everybody was fed by breastmilk, we would never have sons who beat their mothers," said one of the Islamic priests during an interview with investigators.

Most women are already breastfeeding when they are discharged from maternity hospitals. Almost every new mother starts breastfeeding after delivery, but the time of the first breastfeeding depends on hospital practice.

Breastfeeding is seen as a protection of the baby's comfort and happiness: "If my baby laughs during sleep, it means that the Devil came to his dream and said that his mother was dead, but my child laughs and answers him: 'No, my mother is with me—she breastfeeds me.'"

Breastmilk is described as "pure and clean," "natural," "always fresh and sterile," "holy," "costless," and "always ready and always the same temperature." It is viewed also as a medicine. If a baby has an eye infection or a skin irritation, mothers often drop breastmilk into the baby's eyes or onto the skin, believing this will help. Also, breastmilk is reported to "protect against infection," "prevent tummy upsets," and to "cause the baby to grow well and properly."

Mothers reported that children love breastmilk. "Breastmilk is best of all—whatever I feed to my baby, he never falls asleep unless I give him breast." Breastmilk is often seen as the best food nourishment for an infant. The chemical composition of breastmilk was described as "full of perfect vitamins." Secondary ingredients were described as "protein, fat, and carbohydrates." Mothers could not explain the chemical differences between human and cow protein, but they knew that cow's milk is a difficult food for infants and that goat's milk is more like human milk. Most of the women were sure that breastmilk is better than formula or cow's milk for babies, but some worried that because they themselves might not be well-nourished, their breastmilk might not contain as many vitamins as formula. Often, women begin early supplementation with cow's milk, but they do not have a clear understanding of why cow's milk is less desirable, or how early supplementation influences the lactating process. "My milk is watery and my child cries after breastfeeding, but cow's milk is stronger and keeps him full and sleepy for a long time, and I can accumulate my own milk for the next feeding."

Breastfeeding is more than a mere process of giving the baby food, and for some women nourishment may not be the most important factor in breastfeeding. The process of breastfeeding has, for some mothers, a more important function, in that they believe it shapes mother–child relationships: "If you want to make of your child a kind person, let him breastfeed for a long time. It is a holy (sacred) thing." "Breastmilk is part of the mother. Love and tenderness will come to the baby through the milk."

The "holiness" of breastmilk is mentioned often. "Breastmilk is given by God, and a child should be fed by the breasts with love. Even if you don't have milk, breastmilk will be coming." Breastmilk must not be sold or thrown out, or you will be punished by God. "If your baby is satisfied by breastfeeding and you have extra milk, put the extra milk into the soil under the fruit tree, because the tree is also a mother and bears fruit. Thus, you will have enough milk every time, and your baby will be healthy. But if you throw the milk out into the road and people walk through your milk, your child will be ill and your milk will disappear. You must not expose your milk to strange people, or, again, the milk will disappear."

However, when mothers were asked if they would like to breastfeed someone else's child, most of them answered that they would do so with love. "The poor child is not guilty because his mother does not have milk." Others said that they would love to do it, but only if the child's father and father's mother-in-law agreed.* Some mothers rejected breastfeeding somebody else's infant because, they said, their breastmilk was holy and only for their own child.

Most mothers state that colostrum is very beneficial and should be given to the child. This is the case even among those who are confused about the time colostrum begins to flow and the appearance of colostrum. Colostrum (*ogus syt* in Uzbek and *phalla* in Tadjik) is, the mothers note, much more nutritious than breastmilk. They say that infants are quickly satiated by colostrum and sleep for a long time. "Really, colostrum is a gold milk, 100 drops of mature milk is equal to one drop of phalla." One mother's detailed description of the advantages of feeding colostrum was: "An infant who is being fed colostrum is receiving nutrition through every vein, which will last him all his future life—so the child will be cheerful, healthy, and well-developed. That is why colostrum is called 'gold milk.'

* Investigators encountered an interesting example—apparently related to local Islamic tradition—of how the connections between breastfeeding, wet nursing, and blood relationships are perceived. If a mother delivers a baby girl, tradition says that she must not wet nurse another mother's baby boy, because of the possibility that in the future the two children might meet and fall in love. For these children to marry would be considered incest. When two children are fed by one woman's breastmilk the equivalent of a brother-sister relationship is created between them. In the Baghdad Maternity Hospital Islamic priests insist that breastmilk expressed from many mothers should not be intermixed, and that breastmilk expressed from baby girls' mothers should be kept separate from milk expressed from the mothers of baby boys.

Also the color is the same as gold—yellow, thick and sticky. There are much more sugar and calories than in most clean breastmilk."

Reported misperceptions and disadvantages

Although breastfeeding is widespread in Uzbekistan, misperceptions remain common about methods of successful breastfeeding. Although mothers say that if you breastfeed with love you will have milk, most mothers and health professionals strongly believe that the quality and quantity of breastmilk depend on the mothers' diets. This belief is an important factor in choices about breastfeeding during the present economic difficulties, since in this period of growing poverty, doctors state that almost 90% of mothers are anemic and exhausted.

Some traditional beliefs and customs also discourage breastfeeding. For example, breastfeeding during a new pregnancy is not encouraged. "That is not milk; it is dirty water. The child will develop diarrhea." Some doctors told investigators that they sometimes could diagnose a new pregnancy in the mother by symptoms of diarrhea in their breastfeeding infant.

Many believe that insufficient milk or total failure of milk secretion can result from factors such as insufficient food intake by the mother, the mother's temporary weak health, or some unique, long-term, organic weakness of the mother; "evil eye"; or the failure of the mother to adhere to prescribed customs related to female behavior around the time of a birth.

Most mothers told investigators that breastfeeding has many advantages for the child's health, but they could cite fewer advantages to the mother's health. When discussing the health of the breastfeeding mother, most respondents spoke mainly of the feeling of love the mother has for her child during breastfeeding. Although few serious drawbacks to breastfeeding were reported by the mothers, many of them mentioned less serious issues. Breastfeeding was inconvenient if the mother wanted to leave the baby to go shopping or do housework, and it made the mother dependent on the child and the child too closely bonded to the mother.

Some mothers reported that they were ashamed to breastfeed in public. Others said that after a long period of breastfeeding, their child refused weaning food. None of the women claimed that breastfeeding could spoil or had spoiled her own health or figure, but some women reported that they had heard of women who weaned their infants because they worried about their figures. Some doctors worried that prolonged breastfeeding, combined with short spacing between deliveries, could create health problems for women.

Perceived links between mothers' problems with breastfeeding an earlier child and their subsequent inability to breastfeed

Most of the women reported that during pregnancy they did not think so much about future breastfeeding as about their upcoming labor and delivery. The women's attitudes were exemplified by one mother's comments: "I did not worry about breastfeeding. I was sure it would be successful.... I never worried about problems, because as soon as you start to worry about something bad, it is exactly what happens."

However, women who had had problems breastfeeding previous children expected failure with subsequent children. Most reported that they believed that "it is my nature, it usually happens with me." With such an attitude, even a mother who tries to breastfeed may not have enough confidence to do so. Also, she may not receive enough support from her family or community to maintain breastfeeding.

Antenatal preparation

The policies of the Ministry of Health regarding antenatal preparation in Uzbekistan are comprehensive. However, they are often not followed. According to policy, most pregnant women should be under regular observation in antenatal clinics. Doctors encourage women to go to clinics as soon as possible after becoming pregnant. Doctors consider the early identification of pregnant women and their registration at the clinics to be an important means of preventing complications of pregnancy and delivery. About 70% to 80% of pregnant women make their first visit to the antenatal clinic within 12 weeks of conception. Obstetricians and midwives in antenatal clinics check expectant women every 7, 10, or 14 days, or daily if need be, depending on the women's condition. They can also hospitalize women. Every two weeks, expectant women are given urine tests. The most common illnesses reported are anemia, hypertension, and kidney infections. Pediatricians meet with pregnant women twice before delivery to discuss with them their preparation for the new baby.

Beginning at the 32nd week of gestation, women are expected to attend three to five lessons of antenatal "mothers' school" with lectures by an obstetrician or midwife. The lesson topics vary slightly but usually cover basic information about the physiology of pregnancy, hygiene for pregnant women, nutrition during pregnancy, fetal development, prevention of preterm delivery, preparation for labor and delivery, psychological preparation for labor, and infant care. Special lectures on breastfeeding are usually provided. The lectures on birth preparation and hygiene for pregnant women also usually include a little information about the advantages of breastfeeding and preparation of the nipples. In the lessons on the preparation of the mammary glands, women are advised to wash their breasts daily with warm water and soap, dry them with a clean, rough towel, and, during the last period of pregnancy, put petroleum oil onto the nipples and stretch them. The women are advised to air bathe no more than five to ten minutes daily, and to abstain from sexual activities during the first two to three months and the last two months of pregnancy in order to avoid infection.

At the women's consultation sites, lessons regarding infant feeding were observed to be old-fashioned and mostly based on old Moscow recommendations that are now considered inappropriate. For example, women are taught that the first breastfeeding should be 6 to 12 hours after delivery. They are also told that infants should be breastfed six times per day, with four-hour intervals between feedings during the day and six-hour intervals between feedings at night. Early supplementation with additional food is also recommended.

In their antenatal lessons, pregnant women do not receive basic information about lactation management, the correct positioning and attachment of the infant to the breast, the physiology of milk production by the mammary glands, the importance of demand feeding and early breastfeeding, and the importance of exclusive breastfeeding. Also not stressed are the dangers of several bad practices, including the use of pacifiers, early supplementation, and bottle-feeding.

Women who have had previous problems breastfeeding do not receive any practical advice on how to succeed in the future or how to build confidence. On the contrary, they are advised that only a good diet can help. They are further told that bad lactation depends on their physical condition, or on general factors such as poor health, heredity, environment, or stress. A mother may be told that poor lactation or lactation failure is to be expected. It is then suggested that these women try breastfeeding anyway. This approach does not give women any real advice on how to improve their chances for successful breastfeeding and how to build confidence.

Unfortunately, even this type of incomplete and sometimes inaccurate antenatal preparation is given irregularly and sometimes not at all. A major problem is often lack of staff. There are regional variations in available staff at antenatal clinics, maternity hospitals, and children's polyclinics. Required specialist positions are vacant at a rate of 50% to 70%, especially in rural areas and small towns. Therefore, medical staff are too busy with routine work to have time for effective antenatal or postnatal education. There are also communication deficiencies between antenatal, delivery, and postdelivery services.

At the time of this study, Uzbekistan lacked a multisectoral program on breastfeeding education for new mothers or for health professionals. The general attitude appears to be that breastfeeding is natural and therefore there is nothing to learn. Another problem, noted by doctors, but which requires confirmation through analysis of clinic records, is that a growing number of pregnant women do not come into the clinic for discussion, education, or even for treatment in cases of identified anemia. Doctors also say that many women do not come for consultation until the last week of pregnancy, which is too late for education.

Breastfeeding practice

Breastfeeding on demand versus scheduled breastfeeding

After their discharge from the maternity hospital, many new mothers try to maintain the same feeding schedule as they did in the hospital. This is most successful in cases where the baby does not cry and sleeps about three hours between feedings. In most cases, infants cry for a short time after feeding. Most of the mothers interviewed reported that after 10 to 40 days of experimentation with feeding by schedule, they decided to begin demand feeding. "My child did not stay asleep more than one-and-a-half to two hours, cried often from hunger, and could not be calmed. That is why I decided to feed him on demand." Other mothers are prompted by their mothers-in-law: "The child is crying, so he is hungry—let's go and breastfeed him."

Usually mothers who feed their babies on demand do so about 7 to 10 times during a day and 3 to 4 times at night, or fewer times during the day and more at night. One mother reported that she breastfed her baby 28 times, around the clock! Uzbek women do not usually sleep with their infants. Most infants sleep in a special cradle called a *beshik*.*

This practice does not interfere with night feeding. At night the mother sleeps close to the beshik and breastfeeds the baby while reclining beside the cradle. Women told investigators that this is convenient because the beshik has a handle, and the mother can let down her breast into the baby's mouth. She hugs

* The *beshik* (*besik* in Kazahk and Kyrgyz, and *gavara* in Tadjik) is made of wood and is constructed similarly throughout the countries of Central Asia. It is well-adapted to the conditions of nomadic life. The baby inside is tightly held by special restraints made from a wide piece of soft fabric. There is a special wood or bone urine sewer, designed differently depending on the sex of the infant. A urine tube goes down a special hole; urine and feces are collected at the bottom of the cradle. The baby always stays dry and warm. The baby is covered by blankets, and the whole cradle is covered by a special shawl, with the baby sleeping inside.

the beshik around the handle and breastfeeds as long as baby desires. Even if the mother falls asleep, she is sure that the baby will not be hurt. But some children, especially when they are sick, do not want to sleep in a beshik, in which case mothers sleep with their infants during the night.

Most mothers enjoy sleeping with their babies, but worry that this can cause the infant to bond too strongly with the mother. They worry that the baby will not allow them to leave later, even for short times, for housework. Most health professionals are convinced that night feeding and sleeping with the infant are not good, claiming that night feeding can harm the infant's digestive system, that the mother should rest during the night to help lactation, and that sleeping together is not appropriate from a hygienic point of view and could be dangerous for the infant. There were reports of an accident during the last year, in a neighbor's polyclinic, when a mother smothered a baby while asleep. But Uzbek mothers nevertheless sleep with their infants.

Many doctors who know about current recommendations in favor of night feeding and sleeping together by mothers and infants doubt their validity. "Our women are working hard, and if they do not rest during the night they will be exhausted. And it is not hygienic; the infant should have its own bed."

But some doctors, mostly Uzbek rather than Russian, agree with the recommendations. A neonatologist from Vobkent, who was also a 48-year-old mother of four sons, reported: "Of course, I enjoyed sleeping together and night feeding. It is so sweet and lovely to hug my baby all night and feed him. I did it with all my sons, and also it is so convenient and easy. You don't need to get up every time for breastfeeding; you can sleep and feed him at the same time."

The majority of Uzbek mothers—in urban and rural places, younger and older, primaparas and those with many children—prefer demand feeding. The doctors try to persuade women to breastfeed on schedule, but the women do not listen to them. The Uzbek tradition is to feed on demand. Some women doctors who are familiar with new recommendations on demand feeding confessed to us that they have fed their own children on demand and agree that demand feeding is more natural and traditional. "Nothing is new," say these doctors. "Our grandmothers raised children by long breastfeeding, on demand. It is our tradition." In recommendations for mothers, however, health professionals still use the old Moscow instructions and not those rewritten by national specialists in 1996.

Usually the primary sign of a baby's hunger is crying, and the mother can tell whether the baby is really hungry by his or her other behavior: "He looks at me, crying, attracted by my breasts and grasps the breast with greed." The signs by which they know that the baby is sated include leaving the breast of his or her own accord or falling asleep. They do not worry about big or rapid weight gains causing obesity or indigestion. Mothers usually say: "I cannot overfeed my infant by breastmilk. If he gets more than he needs, he burps extra milk; if less, he cries." A more common worry for women is that the child has not gained enough weight or is crying too often from hunger. Many mothers and health professionals do not know the indicators of an adequate intake of breastmilk. They interpret frequent urination, a positive sign for a well-fed baby, as a sign of fatless, watery, and low-nutrition breastmilk, especially if the baby also cries frequently.

The duration of breastfeeding is usually not longer than 10 to 20 minutes, and the baby is often swaddled in a warm blanket for comfort. The baby may fall asleep before he is full of milk, and after a short nap may cry again, and the mother will feed him again. If the baby cries often, mothers begin to worry about the quality or quantity of their milk and begin supplementation. Supplementation is used to keep the baby calm longer or when the mother is busy with housework and cannot breastfeed more often. "I cannot feed him every five minutes," some mothers say. "I should work."

Duration of breastfeeding sessions

Most women indicate a breastfeeding duration of 10 to 20 minutes, with the infants themselves stopping suckling, losing interest, and often falling asleep. If the infant is not satisfied by suckling from one breast or the mother feels discomfort on the one side, she usually gives the infant the other breast. However, many women give the breast for a shorter time, for as little as five to seven minutes. When their infants begin to cry again soon, they do not consider this to be because the breastfeeding session was too short, but because of bad or insufficient milk.

Mothers who breastfeed on demand and who have time and confidence normally do not have difficulties with breastfeeding. In most cases, short-duration feedings are caused by a mother's inability to spend enough time on a breastfeeding session because they are busy with housework. Some Uzbek customs, such as *chilla*,*

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* *Chilla* is from Tadjik *chil*, which means 40. This refers to the 40 days following delivery. During this period, new mothers are expected to follow certain rules: they should stay at home, rest, avoid foreign people, refrain from exposing infants to visitors, eat special foods, abstain from sexual intercourse, not leave the house, not allow infants' clothing to remain out of doors during the dark hours, avoid other women who are in *chilla*, avoid recently married people, and abstain from strenuous housework. Most new mothers practice *chilla* mostly from custom. However, it is a common belief that women who do not follow *chilla* will be punished. That is, the mother or her child will suffer by contracting some disease or getting a rash, or her breastmilk will disappear. It is also believed that evil spirits are waiting to harass such women.

help mothers to concentrate more on babies' needs during the critical period after birth when lactation is established. Chilla provides a good opportunity for new mothers to spend time with their infants in order to bond, to learn to breastfeed, and to establish good breastfeeding habits for later periods when they will be more active.

Most health professionals believe that the optimal duration of a feeding session should be about 20 minutes, as advised in the old Moscow recommendations. This is the amount of time supposedly necessary for infants to consume most of the available breastmilk. It is believed that longer feeding could cause overfeeding, because infants love breastmilk and cannot control the amount they take in. It is also believed that women will become tired or will not have enough time for longer breastfeeding sessions.

Women, on the other hand, generally do not concern themselves with the duration of breastfeeding sessions, but rather see the session as ending naturally with the baby full and not crying. Women speak of the advantages of long breastfeeding sessions mostly in terms of their feelings of love for and bonding with their children. Neither mothers nor health professionals speak about the differences in breastmilk components of "fore" and "hind" milk. Nor do they mention that longer breastfeeding sessions help to support high levels of prolactin secretion. However, both groups agree that it is important to empty the breasts in order to maintain lactation, and see 15 to 20 minutes as long enough to accomplish this.

Weaning time

Long-term breastfeeding is a widespread tradition in Uzbekistan. "My mother has 10 children, my mother-in-law has 8 children and everybody was breastfed." Children and mothers have commonly seen others breastfeeding, including their siblings, friends, and neighbors; breastfeeding is natural and familiar to them. They believe that "a child should be sated—satisfied by breastfeeding for all his future life." Mothers see many advantages to a baby's health and socialization in long-term breastfeeding. "Long breastfeeding is good for babies' health; they will be strong. Through breastmilk love will come between mother and child."

Doctors usually believe that breastfeeding should continue for 1 to 1½ years, but many worry that longer breastfeeding can be harmful to the mother's health. They also are concerned that breastmilk, after 12 months of lactation, is less nutritious and that the baby could become malnourished if he or she prefers breastmilk to the exclusion of other food.

Mothers often say they intend to breastfeed for a long time, but some of them add the qualifier: "If I have milk for a long time." A child is usually weaned at 1½ to 2 years of age, but a mother's last child might be breastfed for a much longer time—for as long as the baby wants, especially if the baby is a boy. One mother breastfed her long-awaited son until he was four years old. Some mothers reported that they breastfed their children even longer. "He was seven years old, coming back from the school and asking for breastfeeding, but privately." If a woman is going to have more children, she will breastfeed until the present child begins teething and the child is able to eat by himself. At that time the child will be weaned, because breastfeeding and pregnancy are not believed to be compatible. Mothers believe lactation to be a means of contraception and use lactation for child spacing.

Breastfeeding during pregnancy is considered harmful to the mother, baby, and fetus. In some cases, mothers reported that they thought breastmilk was affected by pregnancy, that the milk became mildly poisonous, and that consuming such breastmilk could cause diarrhea. Others believed that the breastmilk of pregnant women changed in taste, becoming bitter, and reasoned that if the mother did not stop breastfeeding, the child would wean himself. Also, mothers were of the opinion that the new colostrum that appears in a pregnant mother's breasts belongs to the expected baby. "Nobody should get colostrum twice. This will cause a baby to have diarrhea."

In general, it was seen as difficult for a woman to be pregnant and breastfeed. It is believed that a pregnant woman who breastfeeds would be exhausted and that the fetus would develop more slowly; therefore, she should only breastfeed until the fourth month of pregnancy. In most cases during pregnancy (both planned and unexpected), breastfeeding is stopped. It is very rare for a pregnant woman to breastfeed until her labor.

A religious element, also, has been reported to be a factor in the belief that breastfeeding and pregnancy are incompatible. Some doctors told investigators that it was written in the Koran that women should not breastfeed during pregnancy, and that if they do, they will be punished, and that "women know this." However, no women reported being afraid of this, or that this was a reason not to breastfeed during pregnancy.

Uzbek families are extended and oriented to having many children. Mothers usually say that a family should have at least four children, preferably two boys and two girls. It is important to have a son. A son is the successor and carrier of the family name. He is also expected to remain with the parents throughout his life and care for them in their old age. Daughters are considered guests at home, who will leave their parents upon marriage. A mother without a son will continue to try again until a male child is born.

Doctors reported to the investigators that boys should be breastfed longer than girls, even to 3½ years of age. The reasons given were that the male, in general, is weaker and that early mortality and morbidity are more likely in boys. Most mothers agreed, saying, “Males are weaker than females. A woman has forty lives, but a man has only one life, and boys have more right to breastmilk because they will feed us in old age.” However, many women said that gender does not matter for breastfeeding, and they breastfed girls as well as boys as long as possible.

Use of artificial nipples or pacifiers

Many mothers see no danger in using pacifiers. “How else can I give him water? Of course I will use nipples and bottles.” Some doctors support the mothers, claiming that pacifiers calm the infant, allowing the mother a little rest. However, many doctors are against the use of pacifiers, stating that there is dirt everywhere and that a mother cannot always wash nipples properly. Many mothers claim that they only give their infants pacifiers while they are asleep, especially if the child is formula fed. Some mothers say that children refuse pacifiers on their own, whereas other mothers consider using pacifiers or nipples with bottles undesirable, expressing concern that children might reject breastfeeding after using artificial nipples. Still, most mothers use pacifiers and bottles with nipples from the early stages of lactation up to the infants’ second years.

Exclusive breastfeeding versus supplementation

The practice of “exclusive” breastfeeding is not widespread, but the practice of predominant breastfeeding and water supplementation is more usual in Uzbekistan [1]. Some mothers use predominant breastfeeding longer than necessary, through the child’s seventh or ninth month. Many women state that it is all right to breastfeed a child exclusively, provided that the quantity and quality of the breastmilk are sufficient to satisfy the child’s needs. But these same mothers may give their babies supplementation. The first additional fluid most mothers give is water. Mothers gave the following reasons for giving water to infants: Breastmilk is a food, but water is needed as a fluid for better digestion. Although breastmilk already contains 90% water, breastmilk is still too sweet and fatty; therefore, extra water is necessary. Infants become thirsty just like adults, especially in a hot climate. Water helps prevent rashes and infections in a baby’s mouth. Water helps against constipation and jaundice. The baby will be full longer.

Doctors advise mothers to give fruit juices after three to four weeks as a source of vitamins. They say that the vitamins in mother’s milk are processed through the body and are not as fresh as those straight from fruits. After 1½ to 2 months, babies are given mashed, fresh, boiled vegetables; after four to five months, they are given porridge and cow’s milk; and after six months, they receive family food along with breastfeeding.

Despite a generally positive perception of breastmilk and breastfeeding, at the first sign of insufficient breastmilk production or infant disturbance, doctors and family members often insist on supplementing breastmilk with formula or cow’s milk. Most doctors, mothers, and family members do not clearly understand the damage done to the lactation process by early supplementation. “You should accustom an infant to new food; he will be full longer,” advised one mother-in-law. A doctor advised one mother: “You have insufficient milk supply; your baby is starving. His weight gain is less than normal. You should give the baby supplementation by formula.”

It is rare for doctors to advise frequent breastfeeding as a means of increasing breastmilk supply. Usually mothers are advised to increase food intake, to drink more hot fluids (such as tea with milk and sugar), to drink more milk, and to eat more fatty foods and eggs—even though some of these foods could provoke allergic reactions in some babies by producing food antigens in the breastmilk [2, 3].

In general, mothers believe that babies need breastmilk, water, and fruit juices until six months of age. Mothers believe that babies still need breastmilk after six months but that they should be gradually trained to enjoy the family diet by being given broth, mashed or boiled vegetables, porridge, and meat. By the time their teeth appear, babies should be eating ordinary family foods.

Usually, early supplementation by formula, cow’s milk, and porridge is given to infants in cases of a mother’s insufficient milk production, a baby’s subnormal weight gain according to old Soviet standards, frequent crying, a mother’s need to work or attend school, or a watery or fatless appearance of the breastmilk.

Green stool and skin rash are often considered to be signs of an allergic reaction to breastmilk, and the cessation of breastfeeding will be recommended. Use of commercial formula by nonbreastfeeding mothers is not widespread. Good-quality formula is very expensive. Less expensive formula is of lower quality, and mothers often complain that babies have diarrhea after consuming it. Therefore, they prefer to feed their children cow’s milk or wheat porridge.

Discussion

Problems in understanding breastfeeding

Insufficient breastmilk

Insufficient milk is the most frequently discussed breastfeeding problem among both mothers and doctors. Doctors are generally more worried than mothers about insufficient milk. Almost every health professional told investigators that lack of milk is a widespread problem and that they almost never see mothers who produce breastmilk of good quality and quantity. On the other hand, only about one-third of the women interviewed said they have had problems with decreasing lactation. Only about 11% of the women interviewed had stopped breastfeeding for reasons that include insufficient milk secretion, a new pregnancy, the need to work, and children who refused breastfeeding after being bottle fed.

Not every mother who feels she has decreasing milk secretion stops breastfeeding. In Bukhara, where the health staff is the best informed in the region about breastfeeding, 54% of the women have had problems with insufficient milk secretion, but 50% of these did not stop breastfeeding. Near Bukhara, in Vobkent, 29% of the women reported an insufficiency of milk, but none of them stopped breastfeeding. In Tashkent 13% of the women claimed insufficient milk production, and 100% of these had stopped breastfeeding. However, in Tremez, 33% of the women reported an insufficiency of milk, and only 30% of these stopped breastfeeding. In Angor, a Termes suburb, 57% of women said they have this problem, and only 1% stopped breastfeeding.

Because these ratios are inconsistent, in-depth interviews were conducted. Investigators were told that the effectiveness of various remedies for insufficient milk production depends on the time of onset of the problem. When milk production decreases in the early stages of lactation (during the first one to two months), if doctors do not aggressively advise formula supplementation or mothers-in-law do not aggressively advise supplementation with cow's milk, the mother usually ceases to breastfeed entirely. In cases where milk production decreases during the fourth to sixth months after delivery, simple supplementation normally satisfies the infants, they stop crying, and the mothers usually continue breastfeeding because the infants are experienced at breastfeeding. In most of these later-stage instances, it turns out that what were taken for signs of insufficient milk production were in reality the signs of growth spurts.

In many cases, short growth spurts in infants during early stages of lactation cause a short-term insufficiency in milk. Although more milk will be produced as the baby's demand grows, the short lag in milk production often becomes a misinterpreted signal to mothers and health professionals that supplementation is needed. In most cases in Uzbekistan, women who note a decrease in milk production before the third month are intending to stop breastfeeding and begin bottle feeding. Women who indicate decreased milk production after the fourth to sixth months usually successfully breastfeed longer, because they do not in reality have insufficient milk secretion.

It was learned that most mothers do not understand the indicators of adequate breastmilk production or of sufficient intake by babies. Many doctors, too, interpret a growth spurt as a sign of insufficient milk production if the problem appears during the early stages of lactation. In most cases, correct advice about the early stages of lactation management can help mothers to continue to breastfeed for a long time. Often, mothers conclude that they are producing insufficient breastmilk when their infants show signs such as crying or dissatisfaction after breastfeeding. Other signs by means of which mothers conclude that their lactation is unsatisfactory include lack of fullness in the breasts before breastfeeding; ability to express only small amounts of breastmilk, or an inability to express any milk at all; breastmilk that is light in color, or that has become lighter in color than before; and unsatisfactory weight gain of the infant.

Often doctors contribute to a mothers' anxiety by telling her that if the baby cries a lot, it means that she does not have enough milk. Doctors usually advise controlled breastfeeding in children's polyclinics. If a child's breastmilk intake during controlled breastfeeding is less than optimal (that is, if the monthly weight gain according to the old Soviet weight/age tables is less than normal), supplementation by formula will be implemented. In these cases, babies often cease to breastfeed soon after they begin bottle feeding, especially if they begin bottle feeding in the early stages of lactation.

Most doctors and mothers believe that insufficient breastmilk production is caused by the mother's insufficient food intake or by her eating bad-quality food. People say: "Food now is not good. Everything contains chemicals that weaken women's health. Everybody is anemic. In the past, women delivered at home and never knew anemia."

Another widespread belief is that some women are genetically predisposed to produce small quantities of breastmilk. Stress and anxiety are also mentioned as reasons for low breastmilk production.

Many mothers who breastfeed successfully tell investigators that the amount of milk produced and the overall success of breastfeeding depend on the mother's willingness to breastfeed: "Insufficient breastmilk production is the result of the mother's laziness. It happens because she delays breastfeeding, because she does not really want to. Bottle-feeding is simpler."

However, some women do doubt the influence of food intake on breastmilk production. "Whether I am eating enough or not, I have the same amount of milk. If I eat more, I gain weight, but the milk volume is the same." At the same time, almost all respondents believe that if the mother wants to increase milk production, she should eat more. If this does not help, they think, she must be ill, weak, or genetically predisposed to insufficient lactation.

Women who have had problems breastfeeding previous children often lose confidence during subsequent antenatal periods. A mother in Fergana said: "I was sure that again I would not have milk and that again I would feed my infant by formula, because every one of my children was formula fed. My grandmother told me that if I did not have milk for my two previous children, I would not have milk for my next child. Therefore, it would be better to feed him by formula. So I began artificial feeding. Also, the doctor said to me, 'If you have insufficient milk, it would be better to feed him from the beginning only with formula. It would be hard for his stomach to digest both formula and breastmilk; the child might get ill.'"

Doctors and mothers believe that mothers of twins have insufficient milk as a matter of course. In such cases, doctors usually advise early formula supplementation to ensure proper weight gain for both infants. Those mothers of twins who do breastfeed their babies usually use supplementation as well. However, if the infants are weak or ill, mothers increase breastfeeding.

Uzbeks believe that food has hot and cold properties and that poor health and disease can be caused by an imbalance of hot and cold substances in the body. Insufficient breastmilk production is supposed to be caused by a deficiency in the body's hot properties; therefore, a breastfeeding mother is often advised that for optimal milk production she should consume more foods and fluids with hot properties, such as hot mutton broth, sweet hot black tea with milk, eggs, and rice for fast assimilation. Special nourishing foods called *atalla* are prepared for lactating women, which everyone interviewed told us helps milk production. Fennel and caraway seeds are also given as lactagogues. Some women attribute their lack of success with the use of *atalla* and seeds to their own weak health: they believe their bodies do not react properly. Some said they were too nervous or too busy, or that their infants did not wish to breastfeed because they were being bottle fed.

Both mothers and doctors believe that milk production can be increased by frequent breastfeeding to the point where the mother's breasts are emptied, as well as by eating properly. They also advise that the mother skip one or even a few breastfeedings, giving supplements instead, thus keeping more milk for the next feeding. This is believed to encourage the baby to empty the breasts completely, so that more milk will be produced.

Mothers are often told, to build their confidence, that frequent feeding increases milk production. "The mother should give the breast as often as possible, even in case of low milk production; otherwise, her milk can dry up. It is also important that the woman, herself, should want to breastfeed and love her child, so that she will have milk."

Many misunderstandings about the lactation processes were reported. "It does not make any sense to feed frequently in cases of insufficient milk production. If a mother does not have time to collect enough milk, the baby will remain hungry after feeding, will be upset and crying. On the contrary, the mothers should skip a few breastfeedings, giving supplementation to the baby instead, to allow herself to collect milk for the next feeding."

Misunderstandings of the physiology of lactation, include interpretations of infant weight gain based on out-of-date growth charts and obsolete standards for growth-monitoring, and a lack of good-quality consultations and ongoing support from health professionals.

Quality of breastmilk

Although it is common knowledge that breastmilk is pure, fresh, natural, clean, good medicine, and the best food for infants, many women and health professionals believe that in some cases breastmilk can spoil or develop other quality problems. The issues underlying discussions of breastmilk quality fall into three categories: the definition of good- and bad-quality breastmilk, what might spoil breastmilk, and when breastmilk is not a good food for infants.

There are many opinions on what constitutes good- and bad-quality breastmilk. Most women and health professionals believe that fatty breastmilk is more nourishing and helps children sleep longer and grow faster. Bluish, watery breastmilk is believed to be of bad quality, even though it may be produced in large quantities; the baby will not be satisfied by it and will cry often. In these cases, doctors usually advise supplementation, especially if the child is not gaining much weight. Although too little fat in the milk is considered bad, too much fat is also a disadvantage according to some opinions, because it can cause digestive problems. Then again, one grandmother told investigators that no breastmilk can be of bad quality: all kinds are good simply because they are breastmilk.

The respondents offered many explanations for how they evaluated breastmilk quality, most of which were related to the mother's nutrition and general health. If a mother eats poorly and works hard, they believe she will naturally produce low-quality breastmilk. If a mother eats adequate amounts of food, yet has difficulty breastfeeding, people speculate that the food she eats is bad or that she is unhealthy. If a mother is thin but healthy, her milk is expected to be good; if she is sickly and anemic, her milk is expected to be watery. One mother said: "I am convinced for myself that the quality of breastmilk does not depend on the diet but on the individual. Some women are thin but have good, fatty, thick milk."

Some health professionals are more direct in arguing that there is a relationship between the quality of breastmilk and a mother's diet and health. "What do you want from the woman; what kind of milk can she produce, if her diet is poor and she is anemic? Also pollution and the quality of food are not good. If she does not have stores of vitamins and minerals and her daily diet is not sufficient, what are her sources for breastmilk production? Most women are in poor health, and either they cannot produce enough milk or the milk is not good quality."

Several women interviewed said they were thoroughly confused by doctors' perceptions concerning women's health and well-being, and as a result they had lost their confidence in breastfeeding. "I started supplementation because the doctor told me that my milk was watery. So did my neighbors, but I was in doubt because my baby was growing well. My two previous children are healthy and were breastfed by the same milk," explained a poor single mother of a four-month-old healthy infant.

Mothers' confidence in their ability to produce good milk can also be undermined by close relatives, friends, and neighbors. Said one mother: "My mother-in-law told me, 'your milk is not milk, but slop, and the baby is crying all the time.' "

Mothers reported several opinions about what can spoil the quality of breastmilk. "Different kinds of heat (fever, hot weather, working with hot ovens) or the stagnation of the milk in the breasts (due to engorgement or lack of night feeding) can cause milk to spoil. If the mother has been outside in hot weather, she should express the first part of her milk, because it could be sour. Also, if she was busy with baking in a hot oven, she should express the first part before feeding. If the mother has had fever, her milk will not be good and may taste sour. If she has had engorgement, the first portion of the milk will have been affected and so should be expressed, because it might be sour. In the same way, all 'stagnant' milk will automatically become sour and should be expressed before feeding. If you feed a baby with this spoiled milk, the baby can get diarrhea."

This belief is widespread among mothers and doctors. Some doctors diagnose the causes of diarrhea in infants too quickly, making statements like "Because you breastfed your baby after coming in from the heat, your milk does not appeal to the baby." One mother expressed doubt about this opinion, saying: "Probably, the doctor was right, but I think it happened because of the butter. I was away from home, and my mother-in-law gave butter to my baby in this hot weather. The butter could have been spoiled."

Another common belief, mentioned earlier, is that a new pregnancy spoils the quality of breastmilk because the breastmilk starts to transform into colostrum for the coming baby. The breastfeeding child who ingests this develops diarrhea. Both real and imagined problems with the quality of her breastmilk can cause a mother to stop breastfeeding. "The breastmilk will not be good if the mother has a fever, infection, disease, mastitis—if the breastmilk is contaminated by microbes. If a baby has diarrhea or an allergy, the quality of breastmilk always will be suspect."

Because some doctors are concerned about possible infection, it is standard procedure in hospitals to wash the breasts with soap and water before each feeding. However, this practice can cause soreness and cracking of the nipples while breastfeeding.

Problems with breasts

Mothers say that sore or cracked nipples are the most common breast problem, especially during the first week after delivery, while they are still in the maternity hospital. Other problems reported are engorgement and mastitis. However, mastitis was not often reported in any of the hospitals visited.

Women generally begin their first experience with breastfeeding after delivery in a maternity hospital. Antenatal education on breastfeeding is often poor: even women who do receive a few lessons on breastfeeding and breast preparation often receive outdated information.

According to the instructions from many health professionals, the first breastfeeding sessions should not be longer than three to five minutes, during which time the baby receives its first contact with the mother's colostrum. Mothers are told that longer suckling will cause sore and cracked nipples and that since the mother does not yet have milk, the baby will suck with such energy that the delicate nipple tissue will be damaged. Mothers are also told that poor hygiene causes sore and cracked nipples. Doctors advise mothers to wash their breasts with soap and water, and to rub the nipples with a rough towel before each feeding. "If the mother does not wash her breasts properly, infection in the breasts can result and cause soreness."

Women seldom receive systematic instruction on the correct positioning and attachment of the baby to the breast or how proper attachment can prevent sore nipples. The instruction they do receive is, at best, sporadic and usually given only in response to direct questions. Information on attachment generally includes only that the entire areola and nipple should be placed in the baby's mouth during breastfeeding. Most health professionals interviewed were not well educated on the subject themselves and so they were not able to give mothers good instructions.

Few professionals consider proper attachment and positioning during breastfeeding to be important. Although many women have had episiotomies and cannot sit comfortably because of pain in the pelvic area, they are not advised to lie in a relaxed position. Some are not permitted by doctors to sit at all before having their stitches removed. The practice of tight swaddling also makes proper attachment difficult, because it prevents some babies from opening their mouths properly. Holding the breasts in a "scissors-like" position is encouraged and considered normal.

In cases of sore or cracked nipples, doctors usually advise mothers to continue washing the breasts with soap and water before feeding and to apply a solution of alcohol and "brilliant green" or "permanganate K" ($KMnO_4$) to the damaged breast. After feeding, an application of petrol oil or different kinds of sterilized oils (cottonseed, sunflower, etc.) or antibiotic ointments is prescribed. All such preparations are supposed to be removed before the next feeding by washing the nipples with soap and water again; this was, however, not always carried out. We observed some babies' mouths that were green with Brilliant Green spirit solution.

Application of breastmilk to sore nipples is also practiced, but not as a major therapy. In some severe cases of cracked nipples, a short-term discontinuation of breastfeeding is advised. Most mothers stated that they stopped the practice of washing their breasts before each feeding after their discharge from maternity hospitals, except in cases where they were perspiring after coming in from the heat or cooking near hot ovens. Those who discontinued washing before breastfeeding did so not because they did not believe in its usefulness, but simply because they forgot, did not have time, or lacked hot water at home. The investigators did not see any sore nipples during their observations of home breastfeeding practice.

Because the team observed no actual cases of mastitis in hospitals or at home, they concentrated on protocols for treatment of mastitis. According to health professionals, the main cause of mastitis is poor hygiene. When mastitis occurs, breastfeeding is considered to be contraindicated, and mothers are advised that milk should be expressed and thrown out "because the milk in breasts affected by mastitis is spoiled and contains infection." Women are often afraid to continue or reestablish breastfeeding after recovering from mastitis, because they expect the condition to return.

Breastfeeding in hospitals

In general, breastfeeding in hospitals continues to be conducted according to schedules rather than by demand. Only in rooming-in areas can mothers feed infants on demand. In some older hospitals, where space is limited, rooming-in is implemented by placing mothers' and infants' beds close together. Some health professionals are enthusiastic about on-demand breastfeeding, even where mothers and infants are separated. They tell investigators that they try to send babies to their mothers whenever the babies cry. Still, when asked if they would send a baby to its mother every 15 minutes if it cried that often, they reply that of course they would not; they would send the baby only every two hours. Investigators found many babies in the nursery who showed signs of readiness for breastfeeding (activation of the routine reflex and hypersalivation). Staff members stated that they lacked the special conditions for rooming-in and therefore could not allow it. They also said that they did not allow mothers to come to the nursery for breastfeeding on demand.

Expression of breastmilk is also a routine procedure in hospitals. All mothers express their milk between breastfeedings to be sent to the nursery to feed babies who are separated from their mothers, or for babies of mothers without breastmilk. One mother said: "I was expressing and sending my milk to the nursery for other infants, because when my own infant was in a severe condition after birth, other women were not eager to give their milk to him."

Usually during the first three days after birth, women have a lot of milk, and women express this milk or make an effort to breastfeed other mothers' babies when they are not allowed to feed their own. Also, expression of breastmilk is considered helpful for establishing good lactation. Usually donor milk is collected by a nurse in a special milk room, then pooled, bottled, and pasteurized or sterilized. Feeding is usually done by bottles with nipples.

Uzbekistan's need for a national breastfeeding policy

Uzbekistan needs a more comprehensive and proactive national breastfeeding policy integrated into the different services provided on institutional and community levels. Breastfeeding needs not only to be acknowledged as a salutary practice, but to be actively protected and encouraged. The main reasons include the following:

- Breastfeeding is a strong, positive factor in the health of the infant: it confers short- and long-term protection against acute infectious diseases (diarrhea, otitis media, urinary tract infections, upper respiratory infections, and pneumonia).
- Breastfeeding plays a strong, positive role in the mother–infant relationship.
- Breastfeeding is the mother's right to make an informed choice about how she wishes to feed her infant.
- It is the basic right of the child to have access to the best possible nutrition.
- The practice of breastfeeding is economically beneficial to both the family and the country.
- The practice of breastfeeding is environmentally sound.
- The low rate of exclusive breastfeeding observed in Uzbekistan suggests that this practice requires active encouragement.
- A further decrease in the rate of breastfeeding has been threatened in the Central Asian countries;

therefore the practice of breastfeeding requires active protection.

» Breastfeeding is supported by many initiatives sponsored by international organizations (the Innocenti Declaration, WHO/UNICEF Initiative, WHO/UNICEF, 1991 [4]; the International Code on Marketing of Breastmilk Substitutes, WHO/UNICEF 1981 [5]).

The Almaty Declaration and models for a national breastfeeding policy

The Institute of Nutrition of the Republic of Kazakhstan is responsible for the development and implementation of a national nutrition policy for that country, which is a useful model for other nations in the region, particularly Uzbekistan, which need to create national breastfeeding policies of their own. Kazakhstan's national nutrition policy emphasizes breastfeeding as an important factor in human nutrition.

The International Conference on National Nutrition Policies for Kazakhstan and the Central Asian Republics in the Context of Primary Health Care, held in Almaty, Kazakhstan on 27–28 March 1996, generated an important policy statement, the Almaty Declaration, which led to the inclusion of support of breastfeeding as a key component of the Nutrition Action Plan for Kazakhstan. The Almaty Declaration stresses the importance to the health of both mother and child of exclusive breastfeeding "for the first four to six months of life, followed by timely and appropriate complementary feeding." The Almaty Declaration also stresses that breastfeeding is important to the economies of the Central Asian Republics and Kazakhstan.

The Almaty Declaration further urges that all maternity hospitals should be made baby friendly by "introducing practices that encourage and facilitate breastfeeding, by issuing appropriate decrees and guidelines, by providing for reorientation of health personnel, and by adopting the International Code of Marketing of Breastmilk Substitutes.

The conference's companion document, the Nutrition Action Plan For Kazakhstan, in discussing the causes of poor breastfeeding practice, notes that in Kazakhstan and the Central Asian Republics, most health professionals do not know how to manage successful breastfeeding. Mothers do not receive adequate instruction or encouragement. As a result, initial breastfeeding is often delayed, to the child's detriment. Although most mothers are breastfeeding when they leave the hospital, they encounter difficulties when they go home, because they have received so little instruction or support. In addition, antenatal, delivery, and postnatal breastfeeding support services are uncoordinated.

"The antenatal preparation of pregnant women and perinatal management of new mothers is rigid and outdated," notes the conference's Nutrition Action Plan for Kazakhstan. Postnatal breastfeeding advice, too, is outdated and incorrect. One particular problem is that health workers believe that mothers often have insufficient milk due to poor health or nourishment, although this is not confirmed by survey data. What health workers observe is that by the time their infants are three months of age, 12% of mothers are no longer breastfeeding, and that by six months nearly 30% have ceased [6]. Even in hospitals, babies are given bottle feeds when they cry, although this may not be necessary.

Significance of breastfeeding to the infants, mothers, and national economies of the countries of Central Asia

It is important to support and encourage the tradition of breastfeeding in the Central Asian countries, because of its many health advantages to the infant, particularly within the present Central Asian cultural and economic environment. Because of the antimicrobial factors in breastmilk, infants who are breastfed suffer less frequently from diarrhea and middle ear infections and their resistance is higher to other infections. They are less at risk for undernutrition and for micronutrient deficiencies, including iron deficiency. They also are less subject to allergic responses.

As for benefits to the mother, breastfeeding is both more economical and more convenient, and it facilitates the bonding between mother and child. Moreover, breastfeeding reduces the risk of ovarian and breast cancer and helps in child-spacing. For any nation in Central Asia, a trend toward replacing breastmilk with commercial products or other substitutes would be an intolerable economic, agricultural, and environmental burden. Health-care costs would increase, as well as the costs of infant feeding.

Acknowledgments

This article is based on a joint study of the Kazakhstan Institute of Nutrition, National Academy of Sciences in Kazakhstan, and the Ministry of Health in Uzbekistan. The study was supported by a grant to the International Nutrition Foundation from UNICEF.

References

1. WHO. Indicators for assessing breastfeeding practices. Geneva: World Health Organization, 1991.
2. Kilshaw PJ, Cant AJ. The passage of maternal dietary proteins into human breast milk. Int Arch Allergy Appl Immunol 1984;75,8–15.
3. Gerard JW. Allergy in breastfed babies to food ingested by the mother. Clin Rev Allergy 1984;2:143–9.
4. WHO/UNICEF. Innocenti declaration. The protection, promotion and support of breast-feeding. Geneva: World Health Organization, 1990.
5. WHO. International code of marketing of breast-milk substitutes. Geneva: World Health Organization, 1981.
6. Macro International. Demographic and health survey 1995. Almaty, Kazakhstan: National Institute of Nutrition, Academy of Preventive Medicine, and Calverton, MD, USA: Macro International, 1996.

Erratum

In the article “Effects of salt fortified with iron and iodine on the haemoglobin levels and productivity of tea pickers” by S. Rajagopalan and Malavika Vinodkumar in the *Food and Nutrition Bulletin*, Volume 21, Number 3, pages 323–9, the headings for the control and experimental groups in table 10 on page 328 were inadvertently interchanged. The *Bulletin* regrets this error.

Books received

Complementary feeding: Family foods for breastfed children. Department of Nutrition for Health and Development, World Health Organization, Geneva, 2000. 49 pages, paperback. Sw fr 11.

This small, profusely illustrated book with a simple text provides sound advice and guidance for the use of health workers in advising mothers. Illustrations showing the magnitude of the energy and iron gap at six to eight months are striking. The latter illustrates that the adequacy of iron at zero to five months depends mainly on stores and not the iron in breastmilk. It shows the stores to be completely exhausted at six months, even in infants of normal birthweight. It clearly indicates that complementary food supplying iron must be given by four to six months. It suggests in simple graphics the specific foods to add and the quantities that are appropriate at various months of infancy. WHO is to be congratulated on this clear and useful publication.

The complete handbook of tempe: The unique fermented soy food of Indonesia. Translated and edited by Dr. Jonathan Agranoff, compiled by Dr. Sapuan and Dr. Noer Soetrisno. American Soybean Association Southeast Asian Office, Singapore, 1999. 186 pages, paperback.

Tempe is a soybean product used for centuries in Indonesia and only recently studied scientifically and disseminated to other countries. It is produced by fermentation of soybeans by the mold *Rhizopus oligosporus*. This book provides a comprehensive account of the available information on tempe production and the results of recent research. It provides information that can increase the spread and use of tempe. It also provides an extensive reference list of all relevant literature as a basis for further research. It presents data from original sources with detailed interpretations and suggestions for their application. The chapter on nutritional and health aspects of tempe describes the nutritional composition of tempe and its use in the management of infant diarrhea, lowering cholesterol, and improving dietary iron availability. Those interested in exploring the use of tempe as a good source of protein and a number of other nutrients will find this book useful and complete.

Functions of vitamins beyond recommended dietary allowances. Edited by P. Walter, D. Hornig, and U. Moser. Karger, Basel, 2001. (ISBN 3805570732) 214 pages, hardcover.

Dietary allowances were originally based on avoiding deficiency signs and symptoms. Gradually, as the complexity of vitamin functions and their interactions have become known, these have been taken increasingly into account in discussions of nutrient requirements. Of growing interest are the functions of single nutrients or combinations of nutrients that improve immune function or reduce the risk of chronic diseases. Evidence is accumulating that some vitamins have functions for which requirements are higher than needed for preventing classical deficiencies. The book's 20 chapters, based on a workshop convened by the European Academy of Nutritional Sciences, cover evidence for vitamin functions beyond current recommended dietary allowances, antioxidant vitamins, vitamins and immunocompetence, emerging scientific evidence, and other related topics. It is a convenient and provocative compilation.

Primary and secondary preventive nutrition. Edited by Adrianne Bendich and Richard J. Deckelbaum. Humana Press, Totowas, N. J., USA, 2001. (0-896-03758-4) 465 pages, hardcover. US$99.50.

Preventive nutrition deals with dietary practices and interventions that can prevent the development of disease (primary prevention) and with those that can keep existing disease from becoming worse or can improve their outcome (secondary prevention). This book contains 25 chapters by nearly 50 international experts. Three of these deal with cancer, 10 with cardiovascular and renal disease, diabetes and obesity, 3 with growth immunology and infection, and 2 with bone diseases. The next 6 chapters discuss critical issues for the twenty-first century. They include preventive nutrition issues in ethnic and socioeconomic groups in the United States, micronutrient deficiencies, alcohol, health claims for foods, and dietary supplements. The last chapter by the coeditors introduces an important contemporary concept, the need for preventive nutrition throughout the life cycle. The book also provides a bibliography of books related to both primary and secondary preventive nutrition, lists websites of related interest, and provides an index. It is the single most comprehensive reference source for individuals seeking to improve health outcomes by nutritional improvement. It would also make an excellent text for courses in public health nutrition.

Sight and life manual of vitamin A deficiency disorders (VADD), second edition. Donald S. McLaren and Martin Frigg. Task Force SIGHT AND LIFE, Basel, Switzerland, 2001. (ISBN 3-906412-03-2) 163 pages, paperback.

This is a clearly written, well-illustrated, comprehensive and authoritative presentation of vitamin A in health and disease. It covers the distribution of vitamin A in nature, its bioavailability and distribution in foods, its multiple roles in the maintenance of health, assessment of vitamin A status, xerophthalmia and keratomalacia, morbidity and mortality, interactions with other nutrients, global occurrence, and epidemiology. It reviews the role of retinoids in medicine and has an excellent section on the control of vitamin A deficiency. It also provides a useful reading list, a glossary, 10 pages of references, and an index. This manual is highly recommended.

In Memoriam

Professor Vichai Tanphaichitr, M.D., Ph.D., F.A.C.P, FRACP 1940–2000

The *Bulletin* deeply regrets the untimely death on 29 November 2000 from nasopharyngeal carcinoma of Dr. Vichai Tanphaichitr, one of the outstanding clinical nutrition scientists of Asia.

A medical graduate of Mahidol University in Bangkok, he pursued graduate studies at home and in the United States, obtaining his Ph.D. from Vanderbilt University. In Thailand, he moved between basic and applied nutrition science, public health nutrition, and clinical nutrition and contributed importantly to each of them.

He was a recipient of the Bristol-Myers Nutrition Award and the National Outstanding Researcher Award in Medical Science of the National Research Council of Thailand. He served as President of the Asia Pacific Clinical Nutrition Society (APCNS) and coeditor of the Asia Pacific Journal of Clinical Nutrition (APJCN).

At the time of his death, he was Professor and Chief of the Division of Nutrition and Biochemical Medicine, Department of Medicine (1973–2000), Director of the Institute of Medical Research at Mahidol University, Director of Clinical Nutrition at Ramathibodi Hospital, and Editor-in-Chief of the Thai Journal of Internal Medicine.

Many of his former students now occupy leadership roles in the region. He will be remembered with great admiration and affection by his many colleagues, friends, and students.

Food and Nutrition Bulletin, vol. 22, no. 2

News and notes

Distance-learning courses in nutrition

Compiled by Anne Burgess annburgess@sol.co.uk

The following list was compiled from responses to an e-mail sent to the e-mail discussion group (NGONUT) in which information was requested on distance-learning courses in nutrition suitable for low-income countries. We would be pleased to know of other distance-learning courses in nutrition that exist or are planned.

PG diploma/M.Med.Sci. in Human Nutrition, Sheffield University, UK

Information from Josie Wilson j.wilson@sheffield.ac.uk.

M.Sc. in Human Nutrition at the University of Bridgeport, Connecticut, USA

Information from Michael Giampaoli gmichael@cse.bridgeport.edu or from the University's online campus at www.wcc-eun.com/ub.

Nutrition Rights courses at University of Hawaii at Manoa, USA

The course syllabus is available at www2.hawaii.edu/~kent/pols675cFall2000Syllabus.doc More information can be obtained from George Kent at kent@hawaii.edu.

M.P.H. at Johns Hopkins University, Baltimore, Maryland, USA

Some introductory courses are available through the internet. See http://distance.jhsph.edu/.

Human Nutrition Programme, Deakin University, Australia

Graduate certificate, diploma, and master's courses open to overseas students, even if they are not on e-mail. Contact Prof. Gwyn Jones at gwyn@deakin.edu.au or School of Health Sciences, Deakin University, Geelong, 3217 Australia.

Thanks to Nice Macha in Tanzania who initiated this list.

Source: Field Exchange, ENN, December 2000(11).

Fifth International Graduate Course on Production and Use of Food Composition Data in Nutrition

The Graduate School VLAG (Advanced Studies in Nutrition, Food Technology, Agrobiotechnology and Health Sciences) in Wageningen, the Netherlands, in cooperation with the United Nations University, the Food and Agriculture Organization of the United Nations, and the International Union of Nutritional Sciences, announces the Fifth International Graduate Course on Production and Use of Food Composition Data in Nutrition. The course will be held in Wageningen, the Netherlands, 1–19 October 2001. It is intended for those involved in nutritional database programs as analysts, compilers, or users and will be of value to those teaching nutrition and nutritional aspects of food chemistry.

The aim of the course is to show how those involved in the production of analytical data for nutrients in food, and the compilation of this data into food-composition tables and nutritional databases, contribute to the quality and usefulness of these compilations in nutrition. The course will show how this understanding can be achieved and the benefits that flow from the collaboration of users, analysts, and compilers. Ways in which nutritional databases are used and how these determine the range of nutrients for which values are required and the foods for which values are needed will be reviewed. The choice and validation of analytical methods to give nutritionally relevant values will be discussed.

The course will consist of lectures, seminars, and group work. The course fee, including a Euro 330 nonrefundable deposit, is Euro 3300. The fee covers accommodation and meals at the Wageningen International Congress Centre, course materials, tuition, and excursions. The closing date for applications is 1 July 2001.

Further information can be obtained from Secretariat FoodComp 2001, Wageningen University, Division of Human Nutrition and Epidemiology, P.O. Box 8129, 6700 EV Wageningen, the Netherlands. Telephone (31 317) 485108; fax (31 317) 483342; e-mail foodcomp@info.nutepi.wau.nl. For more information, www.wa.nl/vlag.

Note for contributors

The editors of the *Food and Nutrition Bulletin* welcome contributions of relevance to its concerns (see the statement of editorial policy on the inside of the front cover). Submission of an article does not guarantee publication—which depends on the judgement of the editors and reviewers as to its relevance and quality. All potentially acceptable manuscripts are peer-reviewed. Contributors should examine recent issues of the *Bulletin* for content and style.

Language. Contributions should be in English.

Format. Manuscripts should be typed or printed on a word processor, **double-spaced**, and with ample margins. Only an original typed copy or a photocopy of equivalent quality should be submitted; photocopies on thin or shiny paper are not acceptable.

When the manuscript has been prepared on a word processor, a diskette should be included with the manuscript, with an indication of the disk format and the word-processing program used.

Length. Ordinarily contributions should not exceed 4,000 words.

Abstract. An abstract of not more that 150 words should be included with the manuscript, stating the purposes of the study or investigation, basic procedures (study subjects or experimental animals and observational and analytical methods), main findings (give specific data and their statistical significance if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations. Do *not* include any information that is not given in the body of the article. Do not cite references or use abbreviations or acronyms in the abstract.

Tables and Figures. Tables and figures should be on separate pages. Tables should be typed or printed out double-spaced. Submit only original figures, original line drawings in India ink, or glossy photographs. Labels on the figures should be typed or professionally lettered or printed, not handwritten.

Photographs. Ideally photographic materials should be submitted in the form of black and white negatives or black and white glossy prints. Photographs will not be returned unless a specific request is made.

Units of measurement. Preferably all measurements should be expressed in metric units. If other units are used, their metric equivalents should be indicated.

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References. References should be listed at the end of the article, also double-spaced. Unpublished papers should not be listed in references, nor should papers submitted for publication but not yet accepted.

Number references consecutively in the order in which they are first mentioned in the text. Identify references in the text and in tables and figure legends by arabic numerals enclosed in square brackets. References cited only in tables or figure legends should be numbered in accordance with the first mention of the relevant table or figure in the text. **Be sure references are complete.**

Reference citations should follow the format illustrated below.

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—*standard journal article* (list all authors):

1. Alvarez ML, Mikasic D, Ottenberger A, Salazar ME. Caracteristicas de familias urbanas con lactante desnutrido: un análisis critico. Arch Latinoam Nutr 1979;29:220–30.

—*corporate author:*

2. Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gammaglutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119–25.

Book or other monograph reference

—*personal author(s):*

3. Brozek J. Malnutrition and human behavior: experimental, clinical and community studies. New York: Van Nostrand Reinhold, 1985.

—*corporate author:*

4. American Medical Association, Department of Drugs. AMA drug evaluations. 3rd ed. Littleton, Mass, USA: Publishing Sciences Group, 1977.

—*editor, compiler, chairman as author:*

5. Medioni J, Boesinger E, eds. Mécanismes éthologiques de l'évolution. Paris: Masson, 1977.

—*chapter in book:*

6. Barnett HG. Compatibility and compartmentalization in cultural change. In: Desai AR, ed. Essays on modernization of underdeveloped societies. Bombay: Thacker, 1971:20–35.

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