

Bioavailability of Nutrients and Other Bioactive Components from Dietary Supplements

Bioavailability of Dietary Supplements and Impact of Physiologic State: Infants, Children and Adolescents^{1,2}

Nancy F. Krebs³

Department of Pediatrics, University of Colorado School of Medicine, Denver, Colorado 80262

ABSTRACT Bioavailability can be broadly defined as the absorption and utilization of a nutrient, both of which may be affected by such host factors as gender, physiologic state and coexisting pathologic conditions. This report highlights factors of particular importance for the bioavailability of nutrients for infants, children and adolescents. Considerations for nutrient bioavailability for pediatric populations include maturation of the gastrointestinal tract, growth, character of the diet, and nutritional status. Critical periods of development include early infancy (0–6 mo), late infancy/early childhood (6–24 mo) and adolescence (12–18 yr). Iron, zinc and calcium are minerals of particular interest and importance to pediatric populations and are susceptible to alterations in bioavailability. In the young infant, iron and zinc are highly bioavailable from human milk. By ~6 mo of age, other dietary sources are needed to maintain continued normal status. In breastfed infants who were born prematurely or with low birth weight, earlier supplemental iron is often recommended. For the older infant and toddler, iron and zinc are also important for normal growth and development. The bioavailability of these trace minerals in complementary foods is discussed. During adolescence, adequate calcium intake is critical to normal bone mineralization. In girls, peak calcium absorption and calcium deposition in bones occur at or near menarche, which illustrates the importance of the physiologic state on mineral bioavailability. Investigations into nutrient bioavailability must carefully consider these factors, because the failure to have well-matched comparison groups with respect to age and/or nutritional status may inadvertently mask differences in nutrient utilization. J. Nutr. 131: 1351S–1354S, 2001.

KEY WORDS: • iron • zinc • calcium • bioavailability • infants • adolescents

The concept of bioavailability as applied to nutrients is critically important for understanding nutrient metabolism, homeostasis and, ultimately, requirements. There are numerous factors that affect bioavailability, such as the chemical form of the nutrient, the food or supplement matrix in which the nutrient is consumed and other foods in the diet. There are several host factors that also influence bioavailability, including age, gender, physiologic state and coexisting pathologic conditions. This report highlights the factors of particular importance for bioavailability of nutrients to infants, children and adolescents. Selected principles are illustrated with exam-

ples from three minerals that are commonly of concern at different stages of development: iron, zinc and calcium.

Definition of bioavailability

Bioavailability can be broadly defined as including the absorption and utilization of a nutrient (Fairweather-Tait 1997, O'Dell 1998). Such a definition implies the consideration of more than absorption and includes excretion and retention. Indeed, early descriptions of differences in bioavailability were made from observations that similar total intakes of a nutrient resulted in differences in growth in young animals (O'Dell and Savage 1960). The extent to which nutrient retention is influenced equally by excretion pathways as by absorption pathways will vary among nutrients.

If such a broad definition is used, then the assessment of bioavailability ideally includes more than measurements of absorption efficiency, such as growth, biochemical markers, cognitive development, immune function and others.

Considerations for bioavailability in pediatric populations

There are several factors that may affect bioavailability that apply primarily to infants, children and adolescents, such as increased nutrient requirements to support growth and development, maturation of the gastrointestinal tract and the di-

¹ Presented at the conference "Bioavailability of Nutrients and Other Bioactive Components from Dietary Supplements" held January 5–6, 2000, in Bethesda, Maryland. The conference was sponsored by the Office of Dietary Supplements, National Institutes of Health and the Life Sciences Research Office, American Society for Nutritional Sciences. Conference proceedings are published as a supplement to *The Journal of Nutrition*. Guest editors for the supplement publication were Mary Frances Picciano, Pennsylvania State University, University Park, PA, and Daniel J. Raiten, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

² This work was supported in part by National Institutes of Health Grant DK02240 and by The University of Colorado Pediatric Clinical Research Center, National Institutes of Health Grant MO1RR00069 NCR.

³ To whom correspondence should be addressed at University of Colorado School of Medicine, 4200 East Ninth Avenue, Box C225, Denver, CO 80262. E-mail: Nancy.Krebs@uchsc.edu

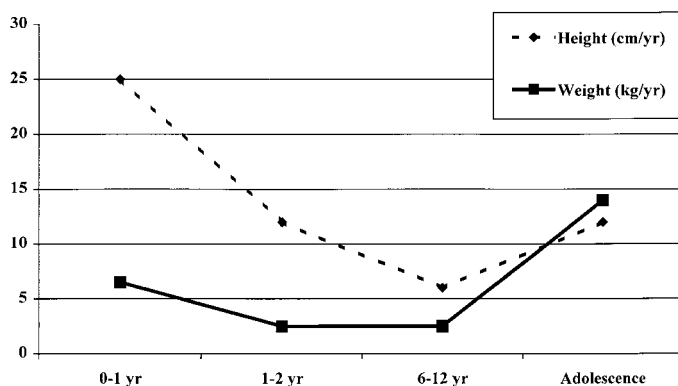


FIGURE 1 Linear and ponderal growth rates.

gestive and absorptive processes, a monotonous diet, age and rates of growth during certain critical periods. It should be noted that other recognized factors that affect bioavailability of nutrients, including such inhibitors of nutrient absorption as phytic and oxalic acids, are not discussed here because they do not affect bioavailability in children differently than they do in adults, although the impact may well be different.

Maturation gastrointestinal function. Although there are only limited data for macronutrient digestion and absorption in the human, information about changes in the absorption of micronutrients with increasing age is even more limited. For protein digestion, trypsin and pepsin activities progressively increase during the first 3 mo of postnatal life. Lactase activity is detectable by 34 wk' gestation and increases thereafter. Pancreatic amylase is not well developed until after the postnatal age of 4 mo, whereas intestinal glucoamylase activity approaches adult levels by 1 mo. Fat digestion is aided by several forms of lipase, including that in human milk, in addition to the relatively modest pancreatic lipase activity. By 6–8 wk of age, fat absorption on a typical high fat milk intake is ~90%. Macronutrient digestion and absorption are thus considered to be essentially mature by the postnatal age of 6 mo (Schmitz 1991). The extent to which gastrointestinal tract maturation influences micronutrient absorption is unknown but is likely to vary with nutrient status, requirements and mechanisms of absorption. The preterm infant poses significant challenges to nutrient absorption that are beyond the scope of this review.

Growth. Growth rates and the accretion of new lean tissue affect nutrient requirements. As shown in Fig. 1, both linear and ponderal growth rates are very rapid in the 1st y of life but steadily decline through the first 3 y of life. During adolescence, there is another significant increase in both height and weight gain. Although the composition of the new

tissue will have an influence on nutrient requirements, for simplicity, it can be concluded that overall nutrient needs will be relatively high during such periods of rapid growth, particularly for nutrients directly involved in musculoskeletal synthesis (Walker and Watkins 1997).

Character of diet. Also important to bioavailability in pediatric groups is the character of their diets. For the young infant in particular, the monotonous nature of the diet results in a somewhat greater risk for nutrient imbalances. For example, in the exclusively breastfed infant, the balance of nutrients in human milk is ideally suited to meet the infant's nutritional needs. If, however, the intake of any of the nutrients is significantly altered, there may be effects on other nutrients that cannot be compensated for by other dietary constituents. The young formula-fed infant is likewise dependent on a single "food," resulting in a critical dependence on the provision of adequate concentrations of all essential nutrients in forms that are optimally bioavailable. The introduction of complementary foods for the older infant begins the process of dietary diversification, but infants and young children commonly continue to consume diets more limited in variety than those of adults. During adolescence, diets often become less than ideal from a micronutrient standpoint, whereas micronutrient needs are increasing in conjunction with increased growth rates, bone deposition, menarche, and so on. Teenagers may choose fad diets or those with limited variability and may rely on high energy, low nutrient-dense food choices. Such dietary practices obviously have implications for micronutrient bioavailability.

Nutritional status. The nutritional status will influence nutrient bioavailability in children, as it does in adults. For studies of bioavailability, it is thus important to have subjects who are carefully matched with respect to their dietary intake and nutrient status. Ferritin levels, as an index of iron status, have been shown to be inversely related to iron absorption (Abrams et al. 1997, Hertrampf et al. 1998).

Critical periods in pediatrics for selected nutrients

As indicated in Table 1, the risk of deficiency is increased at critical ages and for certain minerals. These three micronutrients are discussed as examples to illustrate the considerations presented above at selected critical ages. The choice of minerals as examples for the consideration of bioavailability is appropriate because of their propensity for mineral/mineral interactions and for absorption being affected by other dietary constituents, such as phytic acid.

Birth to 6 mo. For the exclusively breastfed infant from birth to 6 mo of age, both the need for and the supply of iron and zinc change. Healthy term infants are born with iron stores, and the gradual breakdown of red blood cells provides

Table 1
Risk of deficiency at critical ages and for certain minerals

	Nutrient		
	Iron	Zinc	Calcium
Effects of deficiency:	Anemia Mental retardation	Growth retardation Immune dysfunction Developmental delays	Suboptimal bone mineralization
High risk groups	6- to 24-mo-old children Adolescent girls (12–18 yr)	2–24 mo old infants Adolescents (12–18 yr)	Adolescents

another source of utilizable iron. Thus, the dietary iron requirement is modest, and bioavailability of the iron in human milk is favorable. By midway through the 1st y of life, however, intake of an additional source of iron becomes important to avoid the development of iron deficiency. Ferritin levels in infants 6 mo and older are likely to be influenced by the type of early feeding, timing and choice of complementary foods and factors such as birth weight and rate of growth in the first 6 mo of life. Infants who were born prematurely reach their physiologic iron nadir earlier than do term infants; those who are born weighing even a little less than 2500 g also are at a risk of the development of iron deficiency earlier than term infants. In a study of Honduran infants, the introduction of iron-fortified complementary foods at 4 mo did not consistently meet iron needs. Iron supplementation was recommended (Dewey et al. 1998). The American Academy of Pediatrics recommends empirically providing therapeutic iron to such infants, starting at 2 mo post-term, at a rate of 2–4 mg/kg/d, while continuing breastfeeding (American Academy of Pediatrics 1998).

Zinc is another trace mineral that may become limiting for exclusively breastfed infants, but for different reasons. In contrast to iron, zinc concentrations in human milk are initially quite high: 2–3 mg/L, compared with ~0.5–1 mg/L for iron (Siimes and Salmenpera, 1989). These high concentrations decline rapidly over the first few months postpartum and then more gradually from ~4 mo on (Krebs et al. 1995). As for iron, the bioavailability of zinc from human milk is very favorable. By ~6 mo, the adequacy of zinc intake from exclusive breastfeeding becomes more marginal, and the introduction of complementary foods becomes important to maintain normal zinc status (Krebs et al. 1994).

When recommending supplementation of the exclusively breastfed infant with a single mineral, as has been recommended for iron, it is important to consider possible interactions induced by such interventions. Although there have been a small number of studies that examined potential iron/zinc interactions, these have not been in breastfed infants, in whom the normal ratio of iron to zinc is nearly equivalent or, as in the early months of life, the zinc concentration actually exceeds that of iron. The initiation of therapeutic iron supplementation would dramatically change this balance. For example, a 5-mo-old infant that weighed 6 kg would receive 12–19 mg iron/d, while receiving on average slightly <1 mg zinc/d (Krebs et al. 1994). The effects of such an unbalanced intake of trace mineral in breastfed infants has not been examined. In preliminary studies of infants in Denver who were primarily breastfed but also received ~25% of their energy from either low iron (4.5 mg/L) or iron-fortified formula (12 mg/L), fractional absorption of the zinc in human milk was significantly lower in the infants who received the high iron formula (Krebs et al., unpublished data). If confirmed, these findings provide evidence for potentially significant mineral/mineral interactions in a population that has a relatively high requirement for zinc as well as for iron.

Six to 24 mo. The importance of adequate iron and zinc intakes for older infants is recognized to avoid the development of iron deficiency anemia and growth faltering. As noted earlier, the choice of complementary foods is critical to provide adequate intakes of these and other micronutrients. Complementary foods that are commonly recommended for early consumption are often quite high in iron due to fortification but tend to be much lower in zinc (Krebs 2000).

A number of investigators have examined the absorption of iron from weaning foods. The effect of meat or heme concentrate on the absorption of nonheme iron has been evaluated

with inconsistent results. Engelmann et al. (1998) examined the incorporation of stable isotopes of iron into erythrocytes in 6- to 7-mo-old infants from a vegetable puree meal with or without added meat (lean beef). In this study, there was a significant enhancement of nonheme iron absorption with the addition of meat. In a different study design, Martinez et al. (1998) evaluated the potential effect of heme iron concentrate as a fortificant for weaning foods in 6-mo-old infants. Iron retention based on 7-d balance data did not differ for those receiving heme iron concentrate compared with those receiving ferrous sulfate, nor did the heme iron significantly increase the absorption of iron stable isotope administered as ferrous sulfate. The interpretation of this study is complicated by the small number of subjects who were studied with the stable isotope. The groups differed with regard to formula or breastfeeding, which would likely affect iron status and therefore iron absorption. In another study of mineral absorption in 5- to 7-mo-old infants, the absorption of iron from labeled ferrous sulfate was inversely related to serum ferritin, whereas iron absorption from human milk was not related to ferritin levels (Abrams et al. 1997). The percentage of iron absorption from human milk, ~21%, was lower in these older infants than is frequently assumed (~50%). Whether the age of the infants, routine consumption of beikost or other factors were key to this observation is unknown.

Fewer studies have examined zinc absorption from complementary foods. We compared the fractional absorption of zinc from meat (beef) and from iron-fortified cereal in 7-mo-old breastfed infants. Although the absorption efficiency did not differ between the two foods, the significantly higher zinc content of the meat resulted in higher amount of zinc absorbed (Jalla et al. 1998). Abrams et al. (1997) also examined zinc absorption from human milk in 5- to 7-mo-old infants who were also consuming beikost. The authors reported fractional absorption values that were similar to those observed for exclusively breastfed infants and found no relationship between percent absorption and the zinc intake from beikost; detailed information on the sources of nonhuman milk zinc was not provided.

Adolescence. The importance of calcium intake during adolescence to optimize bone mineral accretion has gained considerable attention in recent years (National Institutes of Health 1994). Because many adolescents do not routinely consume calcium in amounts that are optimal for bone mineralization, recommendations have been made to increase intake through the use of supplements. It is also now recognized that calcium absorption, and therefore bone mineral accretion, is intimately related to stage of pubertal development. In a large cross-sectional and partially longitudinal study of calcium metabolism in 5- to 18-y-old girls, Bronner and Abrams (1998) reported that calcium absorption, bone calcium deposition and bone calcium removal all peaked at or near menarche. Both deposition and removal were linearly related to calcium absorption. Likewise, another group reported on axial and peripheral bone mineral density in ~300 children aged 6–18 y and found that pubertal stage was the strongest predictor of axial bone mineral density (Rubin et al. 1993).

These observations illustrate the critical importance of the pubertal stage in considering calcium bioavailability in children. When comparing absorption and bioavailability of different sources of calcium, such as supplements, subjects must be well matched to ensure valid conclusions are reached. In addition, other factors that are likely to be important include the source of the calcium (e.g., inorganic supplement, vegetable based or dairy product), vitamin D status, physical activity

level, ethnicity and possibly intakes of protein, fat, sodium and other minerals.

This overview highlights the importance of considerations for bioavailability of nutrients and dietary supplements specific to pediatric populations. Although infants and children do not routinely take dietary supplements on their own, caution should be exerted when making public health recommendations. For minerals in particular, there is potential for nutrient/nutrient interactions that may compromise bioavailability of one mineral while focusing on another.

Areas for future research include more comprehensive evaluations of bioavailability, because for some nutrients, fractional absorption provides only partial insight into nutrient utilization. As illustrated by the effects of iron supplementation on zinc absorption, more systematic investigation of nutrient/nutrient interaction is needed, especially as the use of dietary supplementation becomes more common. When possible, an assessment of the bioavailability in terms of functional outcomes would also be beneficial. Such outcomes might include effects on growth, development and cognitive function and immune function. Such broader assessments would provide more useful information than simple comparisons of the absorption of a given nutrient. Finally, supplementation programs have the potential for unforeseen adverse consequences, and these programs should also be examined when intakes of supplements exceed amounts that would normally occur in the diet. This is particularly important for pediatric populations.

LITERATURE CITED

- Abrams, S. A., Wen, J. & Stuff, J. E. (1997) Absorption of calcium, zinc, and iron from breast milk by five-to seven-month-old infants. *Pediatr. Res.* 41: 384-390.
- American Academy of Pediatrics, Committee on Nutrition (1998) *Pediatric Nutrition Handbook*, 4th ed. (Kleinman, R. E., ed.), American Academy of Pediatrics, Elk Grove Village, IL.
- Bronner, F. & Abrams, S. A. (1998) Development and regulation of calcium metabolism in healthy girls. *J. Nutr.* 128: 1474-1480.
- Dewey, K. (1998) Effects of age of introduction of complementary foods on iron status of breast-fed infants in Honduras. *Am. J. Clin. Nutr.* 67: 878-884.
- Engelmann, M. D., Davidsson, L., Sanstrom, B., Walczyk, T., Hurrell, R. F. & Michaelsen, K. F. (1998) The influence of meat on nonheme iron absorption in infants. *Pediatr. Res.* 43: 768-773.
- Fairweather-Tait, S. J. (1997) From absorption and excretion of minerals. . . to the importance of bioavailability and adaptation. *Br. J. Nutr.* 78(suppl): S95-S100.
- Jalla, S., Steirn, M. E., Miller, L. V. & Krebs, N. F. (1998) Comparison of zinc absorption from beef vs iron fortified rice cereal in breastfed infants. *FASEB J.* 12: A346.
- Krebs, N. F. (2000) Dietary zinc and iron sources, physical growth and cognitive development of breastfed infants. *J. Nutr.* 130: 358S-360S.
- Krebs, N. F., Reidinger, C., Robertson, A. D. & Hambidge, K. M. (1994) Growth and intakes of energy and zinc in infants fed human milk. *J. Pediatr.* 124: 32-39.
- Krebs, N. F., Reidinger, C. J., Hartley, S., Robertson, A. D. & Hambidge, K. M. (1995) Zinc supplementation during lactation: effects on maternal status and milk zinc concentrations. *Am. J. Clin. Nutr.* 61: 1030-1036.
- Hertrampf, E., Olivares, M., Pizarro, F. & Walter, T. (1998) High absorption of fortification iron from current infant formulas. *J. Pediatr. Gastroenterol. Nutr.* 27: 425-430.
- Martinez, C., Fox, T., Eagles, J. & Fairweather-Tait, S. J. (1998) Evaluation of iron bioavailability in infant weaning foods fortified with haem concentrate. *J. Pediatr. Gastroenterol. Nutr.* 27: 419-424.
- NIH Consensus Statement (1994) Optimal Calcium Intake. Bethesda, MD: NIH 12:1-31.
- O'Dell, B. L. (1998) Personal reflections on a galvanizing trail. *Annu. Rev. Nutr.* 18: 1-18.
- O'Dell, B. L. & Savage, J. E. (1960) Effect of phytic acid on zinc availability. *Proc. Soc. Exp. Biol. Med.* 103: 304-306.
- Rubin, K., Schirduan, B., Gendreau, P., Sarfarazi, M., Mendola, R. & Dalsky, G. (1993) Predictors of axial and peripheral bone mineral density in healthy children and adolescents, with special attention to the role of puberty. *J. Pediatr.* 123: 863-870.
- Schmitz, J. (1991) Digestive and absorptive function. In: *Pediatric Gastrointestinal Disease* (Walker, W. A., Durie, P. R., Hamilton, J. R., Walker-Smith, J. A. & Watkins, J. B., eds.), pp. 266-280, B.C. Decker Inc., Philadelphia, PA.
- Siimes, M. A. & Salmenpera, L. (1989) The weaning: iron for all or one. *Acta Paediatr. Scand. Suppl.* 361: 103-108.
- Walker, W. A. & Watkins, J. B. (1997) *Nutrition in Pediatrics: Basic Science and Clinical Applications*. B. C. Decker Inc., Hamilton, Ontario, Canada.