Overview of Zinc Absorption and Excretion in the Human Gastrointestinal Tract

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ABSTRACT Zinc homeostasis is primarily maintained via the gastrointestinal system by the processes of absorption of exogenous zinc and gastrointestinal secretion and excretion of endogenous zinc. Although these processes modulate net absorption and the size of the readily exchangeable zinc pools, there are limits to the effectiveness of the homeostatic mechanisms of these and other systems. As a result of the interplay of the subcellular regulation of these mechanisms and host, dietary and environmental factors, zinc deficiency is not uncommon, especially on a global basis. This overview briefly reviews current understanding about the subcellular mechanisms of zinc absorption and transport. Factors recognized to affect zinc absorption at the whole body level are reviewed and include the amount and form of zinc consumed; dietary promoters, such as animal protein and low-molecular-weight organic compounds; dietary inhibitors, such as phytate and possibly iron and calcium when consumed as supplements; and physiologic states, such as pregnancy, lactation and early infancy, all of which increase the demand for absorbed zinc. The control of endogenously secreted zinc is less well understood. Available data suggest that the quantity of secreted zinc with each meal may be considerable and that efficient reabsorption is critical to the maintenance of normal zinc balance. Factors that have been proposed to interfere with the normal reabsorption of endogenous zinc include phytate and unabsorbed fat. Understanding of the dietary, physiologic, pathologic and environmental factors that may adversely affect these processes, and therefore zinc homeostasis, will be critical to preventing and treating zinc deficiency in human populations.

KEY WORDS: zinc absorption, zinc homeostasis, metallothionein, zinc transporters, zinc intake

A number of physiologic systems contribute to zinc homeostasis under different conditions (King 1986, Wastney et al. 1986). Central to maintenance of zinc homeostasis, however, is the gastrointestinal system, especially the small intestine, liver and pancreas. Specifically, both the processes of absorption of exogenous zinc and gastrointestinal secretion and excretion of endogenous zinc are critical to whole body zinc homeostasis.

Although data from traditional balance studies suggest the effectiveness of these homeostatic mechanisms over a wide range of dietary zinc intake (King 1986), it also seems clear that there are limits to adaptation. For example, although “balance” may be achieved on a marginal intake, there may be compromise in some critical functions dependent on zinc, such as growth and immune function. Likewise, from studies in healthy infants, in whom there can be a very wide range of dietary zinc intake at the same age depending on whether the intake is from human milk or formula, the homeostatic mechanisms considerably narrow the net “balance.” Nevertheless, those with a high intake tend to have higher net absorption (Krebs et al. 1996, 1999). Whether this results in higher tissue levels or exchangeable pools that can be accessed in times of deprivation or increased need is not known.

As discussed elsewhere in the supplement, mild zinc deficiency is likely to be quite widespread in certain vulnerable groups: those with high physiologic requirements such as infants and young children, pregnant and lactating women and individuals chronically on low zinc intakes or diets with poor zinc bioavailability. These observations emphasize that there are limits to the effectiveness of the homeostatic mechanisms. Much remains to be learned about the homeostatic mechanisms themselves, their control and the interplay of host, dietary and environmental factors, which in certain circumstances results in suboptimal zinc status of the individual.

This overview briefly addresses the homeostatic processes in the gastrointestinal tract in relation to present knowledge in normal and pathologic conditions.

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3 Abbreviations used: MT, metallothionein; ZnT, zinc transporters.
Absorption of exogenous zinc

Subcellular processes. Absorption can be considered as the processes of influx into the enterocyte and through the basolateral membrane and of transport into the portal circulation. The subcellular mechanisms of uptake of exogenous zinc remain to be elucidated, but both saturable and unsaturable processes are still thought to be involved (Lonnernald 1989, Reyes 1996). The recently characterized zinc transporters (ZnT) have significantly increased understanding of the interrelationships of cellular zinc uptake and efflux but do not yet account for observations at the whole body level. ZnT-1 is a ubiquitously expressed protein that has been found to be present in the villi of the proximal small bowel (McMahon and Cousins 1998a). In response to manipulation of dietary zinc, however, expression in rats was increased in response to zinc supplementation but not to zinc restriction (McMahon and Cousins 1998b). These and other observations have led to a current consensus that ZnT-1 functions mainly as a zinc exporter and may play a role in zinc homeostasis as a mechanism for zinc acquisition and elimination under conditions of excess of zinc (McMahon and Cousins 1998b).

The role of metallothionein (MT), an intracellular metal binding protein, in the regulation of zinc absorption, particularly in conjunction with the zinc transporters, also remains unclear. Hepatic and intestinal MT synthesis is stimulated by dietary zinc supplementation, by intraperitoneal zinc injection and by inflammation and the acute phase response. Dietary restriction also results in diminished MT synthesis. In experiments with knockout and transgenic mice, the rise in serum zinc after a single dose of zinc was much greater in the MT knockouts than in the control animals. In contrast, the serum zinc response of the MT transgenic animals was blunted compared with that of the control animals. The expression of ZnT-1 was also measured and found to be directly related to serum zinc levels but unaffected by MT levels (Davis et al. 1998). Thus, MT may function in cellular responses to limit free zinc concentrations within quite narrow ranges (Cousins 1996) and function as a zinc pool (Davis et al. 1998). Another transporter potentially involved in zinc and other metal uptake is DCT1, a transmembrane polypeptide that is found in the duodenum in the crypts and lower villi and may be involved for the uptake of several metal ions (McMahon and Cousins 1998).

As these transport proteins are identified and characterized, investigations in the whole animal, under conditions of a range of dietary intake, will be needed. Animal and human studies indicate considerable ability to enhance efficiency of absorption in response to low dietary zinc intake or increased physiologic demand; as yet, the subcellular correlates of these observations are lacking. Observations relating the amount of absorbed zinc to the amount of excreted zinc and to exchangeable pool sizes also await corroboration with the subcellular processes.

Whole body processes. The primary site of absorption of exogenous zinc in the human is thought to be in the proximal small bowel, either the distal duodenum or proximal jejunum (Krebs et al. 1998, Lee et al. 1989). Factors known to influence absorption include the amount of zinc present in the intestinal lumen; the presence of dietary promoters (e.g., human milk, animal proteins) or inhibitors (e.g., phytate, other minerals); zinc “status,” especially in relation to chronic zinc intake; and physiologic states.

Amount and form of zinc. Absorption studies in animal models indicate an inverse relationship between percentage absorption and dietary zinc intake (Coppen and Davies 1987, Jackson et al. 1981). At extremely high intakes, however, absorption efficiency was no longer affected and the animals relied on excretion primarily to regulate zinc homeostasis. In humans, limited data also support a similar relationship to dose/intake, which is further affected by whether extrinsic zinc is administered during a meal or in the postabsorptive state with water alone (Sian et al. 1993). In the postabsorptive state, absorption was unaffected by doses up to 5 mg but declined by 20–30% with a 10-mg dose. When the dose was administered with a meal, however, fractional absorption was lower with both 3- and 5-mg doses compared with 1 mg. These authors hypothesized that the different observations between the postabsorptive state and with the meal are due to the competition for absorption of exogenous zinc with endogenously secreted zinc in conjunction with a meal. In this and other studies, even as the fractional absorption declines, the actual amount of absorbed zinc increases with the increasing amount of zinc present (Istfan et al. 1983, Jackson et al. 1984, Sian et al. 1993, Ziegler et al. 1989).

Intraluminal zinc is present in several different forms after a meal as a result of digestive processes that release zinc from food components and endogenously secreted zinc. The free zinc forms complexes with ligands such as amino acids, phosphates and other organic acids. A discussion of the differences in availability of various zinc salts used as supplements is beyond the scope of this review. Briefly, the absorbabilities of zinc sulfate and zinc acetate appear to be comparable and quite favorable. In contrast, zinc oxide and zinc carbonate are relatively insoluble in aqueous solutions and result in considerably lower absorption by postconsumption plasma zinc measurements. The implications of these findings for supplementation programs have been reviewed recently (Allen 1998).

In experimental conditions, the efficiency of absorption responds quite promptly in humans to changes in dietary zinc intake, approaching 90% during severe restriction (Jackson et al. 1984, Istfan et al. 1983, Wada et al. 1985). Other observations under experimental conditions, however, suggested that during 6 mo of a moderately zinc-restricted diet in normal volunteers, the initial response of increased absorption was not sustained beyond the first 2–4 mo of restriction (Lee et al. 1993). Further evidence that absorption may not be a long-term adaptation is provided by findings in populations with chronically marginal intake. In a comparison of two groups of Chinese women on monotonous diets, fractional absorption was not higher in women on a low intake (5 mg/d) compared with those with a higher usual intake (8 mg/d) (Sian et al. 1996). Although it has been suggested that the absorption process provides a “large capacity” adaptation to fluctuations in zinc intake, these data from long-term zinc depletions studies, both experimental and population based, suggest that adaptation of zinc secretion and excretion may be more sustained and may provide a further refinement in the control of homeostasis (Lee et al. 1993, Sian et al. 1996).

Dietary promoters and inhibitors of zinc absorption. These factors are discussed in more detail in other sections but for completeness are briefly mentioned here. The amount and type of protein affect zinc absorption. For example, the presence of even modest amounts of animal protein can substantially enhance the efficiency of absorption, in addition to increasing the absolute amount of zinc (Sandstrom et al. 1980). Soluble, low-molecular-weight organic substances, such as the sulfur-containing amino acids and hydroxy acids, bind zinc and facilitate its absorption (Lemond 1989).

Insoluble hexaphosphates and pentaphosphates (phytic acid) bind zinc and form poorly soluble complexes that result in reduced absorption of zinc. Phytate is found in varying
amounts in plant products, with grains and legumes having especially high levels. Fractional absorption of zinc is negatively associated with the phytate content (Sandstrom and Lonnerdal 1989). On a global basis, plant-based diets with high phytate-to-zinc molar ratios are considered to be the major factor contributing to zinc deficiency (Gibson, 1994).

Interactions between zinc and other minerals remain a concern, particularly with the liberal use of supplements in the United States. Iron and calcium in particular are of practical interest. A number of studies have demonstrated a negative impact of therapeutic supplemental iron on plasma zinc levels, e.g., during pregnancy (Breskin et al. 1983, Hambidge et al. 1983, 1987) and on absorption during lactation (Fung et al. 1997). Situations that seem most likely to encounter problematic interactions are those in which the iron is administered in solution or as a separate supplement rather than incorporated into a meal (Whittaker 1998). Because mineral supplementation programs are designed for populations at risk of both iron and zinc deficiencies, clarification of both quantitative and qualitative aspects of potential interactions will be critical. Calcium, especially in the presence of phytate, also may interfere with zinc absorption (Oberleas et al. 1966). Data from human balance and absorption studies in adults have been conflicting with respect to adverse effects of calcium supplementation on zinc homeostasis (McKenna et al. 1997, Wood and Zheng 1997).

**Physiologic states.** Those generally associated with increased efficiency of fractional absorption are ones in which the requirement is high, such as infancy, pregnancy and lactation. The young exclusively breast-fed infant provides an excellent example of very high fractional absorption, with an average absorption of 0.55, which is approximately the rate of absorption of zinc administered alone with water (Krebs et al. 1996). This efficiency is likely due to several factors, including the complex organic matrix of human milk, the modest concentrations of zinc and other minerals and the effect of the high physiologic requirement for zinc during a period of rapid growth. The latter point is supported by measurements in adults of zinc absorption from human milk, which was very low in these subjects than in infants (Sandstrom et al. 1983).

Fractional absorption may increase modestly during human gestation to meet the needs of the fetus and maternal tissues: about 0.25 mg/day of additional absorbed zinc for humans (Swanson and King 1987). In a longitudinal study through the reproductive cycle, about half of a group of well-nourished women had some increase in fractional absorption from preconceptional baseline measurements to measurements in the third trimester. The mean values of fractional absorption, however, were not significantly different at the two time points (Fung et al. 1997). Such observations may reflect the variability in dietary zinc intake, differences in zinc status and the relatively small estimated increase in need. Studies in women with more marginal dietary zinc intake will be important to better understand the capacity for enhanced fractional absorption during pregnancy. Zinc supplementation trials in high risk populations have demonstrated positive effects on pregnancy outcomes, suggesting a preexisting zinc deficiency (Caulfield et al. 1999, Goldenberg et al. 1995) and providing another example of the limits of adaptation.

In contrast to pregnancy, a significant increase in fractional absorption during early human lactation has been reported by several investigators (Fung et al. 1997, Jackson et al. 1988, Moser-Vellon et al. 1996). This is consistent with the fact that the amount of zinc excreted daily in breast milk in the first few months postpartum is at least twice that deposited in fetal tissue during late gestation (King and Turnlund 1989, Krebs et al. 1995). The most dramatic increases were seen in a group of low-income lactating women in Brazil who also had very low dietary zinc intakes (Jackson et al., 1988). In the longitudinal study of zinc absorption through the reproductive cycle in well-nourished U.S. women, the mean at 7–9 wk postpartum was ~75% higher than the preconception measurement. Iron supplementation of ~60 mg/day in a subgroup of the lactating women was associated with no increase in fractional zinc absorption, providing evidence for an interference with zinc absorption at routine levels of iron supplementation (Fung et al. 1997).

**Secretion, reabsorption and excretion of endogenous zinc**

The processes of secretion and reabsorption or excretion of intestinal endogenous zinc have not been well characterized in humans. There are several potential sources of the endogenous zinc: pancreatic and biliary secretions, gastroduodenal secretions, and sloughing of mucosal cells. Measurements in humans of endogenous intestinal zinc have primarily been made as fecal excretion; these indicate that amounts excreted are responsive to zinc intake, absorbed zinc and physiologic need. As noted earlier, in populations with chronically low dietary zinc intake, conservation of endogenous zinc may be more critical to the maintenance of zinc homeostasis than the adaptation in fractional absorption (Lee et al. 1993, Sian et al. 1996). Efficient conservation of endogenous zinc has also been found to be critical for breast-fed infants. In addition to favorable absorption of zinc in human milk, the achievement of positive net absorption is dependent on modest losses of endogenous zinc (Krebs et al. 1996).

The quantity of endogenous zinc secreted with each meal is likely to be considerable; preliminary data indicate the amounts may be comparable to or exceed the amount of exogenous zinc (Krebs et al. 1998, Matseshe et al. 1980). The regulation of the quantities of zinc secreted is presently unknown, but if the preliminary quantitative findings are confirmed, maintenance of zinc balance would thus be dependent not only on absorption of some fraction of exogenous zinc but also on efficient reabsorption of the endogenous zinc. Preliminary evidence from intestinal intubation studies suggests that reabsorption may continue more distally in the small bowel than absorption of exogenous zinc (Krebs et al. 1998). The mechanism of such reabsorption has not been specifically investigated but may also be influenced by the form and quantity of the zinc, intraluminal factors and the site in the small bowel.

The presence of intraluminal factors, such as dietary phytate or unabsorbed fat, may interfere with efficient reabsorption and cause essentially a “leaching” of zinc from the body. Observations consistent with this have been made in infants with fat malabsorption (Krebs et al. 1999), and studies are under way to examine the possible adverse effect of dietary phytate on reabsorption of endogenous zinc. It is also possible that pathologic conditions that affect the gastrointestinal tract, perhaps especially in the distal small bowel, have adverse effects on zinc nutriture because of interference with the normal conservation of endogenously secreted zinc.

**Areas for future research**

Areas for future research include further characterization of the normal processes in the gastrointestinal tract, including both absorption and excretion, which are critical to maintenance of zinc homeostasis in response to wide ranges of zinc...
intake. The mechanisms of regulation of these processes and identification of their regulatory signals at the cellular as well as the whole body level also merit more investigation. An understanding of the dietary, physiologic, pathologic and environmental factors that may adversely affect these processes, and therefore zinc homeostasis, will be critical to preventing and treating zinc deficiency in human populations.

LITERATURE CITED