Zinc Homeostasis in Humans

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ABSTRACT Maintaining a constant state of cellular zinc nutrition, or homeostasis, is essential for normal function. In animals and humans, adjustments in zinc absorption and endogenous intestinal excretion are the primary mechanisms for maintaining zinc homeostasis. The adjustments in gastrointestinal zinc absorption and endogenous excretion are synergistic. Shifts in endogenous excretion appear to occur quickly with changes in intake just above or below optimal intake. The absorption of zinc responds more slowly, but it has the capacity to cope with large fluctuations in intake. With extremely low zinc intakes or with prolonged marginal intakes, secondary homeostatic adjustments may augment the gastrointestinal changes. These secondary adjustments include changes in renal zinc excretion, a shift in plasma zinc turnover rates and, possibly, an avid retention of zinc released from selected tissues, such as bone, in other tissues to maintain function. J. Nutr. 130: 1360S—1366S, 2000.

KEY WORDS: • zinc • zinc homeostasis • zinc absorption • zinc kinetics • zinc excretion

The ability to maintain a constant internal state with varying external conditions is essential for survival. This is called homeostasis if the nutrient flow within an organism is in a state of equilibrium, and it is called homeoeosis if there is continual retention of the nutrient as occurs during growth, reproduction or lactation (Kirchgessner 1993). Changes in zinc absorption and excretion in the gastrointestinal tract are the primary mechanisms for maintaining zinc homeostasis. Adjustments in renal excretion also occur with extremely low or high intakes of zinc. Tissue and cellular redistribution of zinc may contribute further to the maintenance of zinc homeostasis. The purpose of this report is to describe how these adjustments in zinc homeostasis occur in animals and humans.

Changes in zinc intake and whole body zinc content

Studies in experimental rats demonstrate a capacity to maintain a relatively constant content of zinc in the whole body while dietary zinc intakes vary by as much as 10-fold (Kirchgessner 1993). When the zinc intakes of weaning experimental animals ranged from 10 to 100 mg/kg, the content of the whole body zinc content remained constant at ~30 mg/kg. Changes in the concentration of zinc in the whole body changed only when very low (<10 mg/kg) or very high (>100 mg/kg) intakes were consumed. The homeostatic mechanisms were insufficient to maintain body zinc content with these extremes in intake, and there was either a loss or an accumulation of zinc within the body.

In humans, the effect of changes in dietary zinc on whole body zinc content cannot be measured directly. Measurements of zinc balance, however, provide a means for estimating changes in whole body zinc content with changes in intake. Typically, human zinc intakes range from 107 to 231 μmol/d; this is equivalent to ~14–30 mg/kg for comparison with rat diets. These intakes support crude zinc balance (i.e., replace fecal and urinary losses) in healthy adults, but balance cannot be achieved when as little as 22 mmol/d (2.8 mg/kg) or as much as 306 μmol/d (40 mg/kg) is fed (Johnson et al. 1993). With these extreme reductions or increases in zinc intake, zinc losses either fell or increased during the first 6–12 d after the dietary change so that balance was achieved. Thus, humans appear to have the capacity to regulate whole body zinc content over a 10-fold change in intake, as has been observed in experimental animals.

Intestinal regulation of zinc homeostasis

The gastrointestinal tract is the major site for regulation of zinc homeostasis. The mechanism involves adjustments in both zinc absorption and endogenous excretion into the feces. It is important to remember, however, that zinc absorption and endogenous excretion cannot be measured directly in animals or humans. All determinations are based on models that cannot be validated. Nevertheless, consistent results across studies lend confidence to the validity of the estimates.

In detailed metabolic balance studies in rats (Weigand and Kirchgessner 1978), the efficiency of zinc absorption decreased...
fluctuations in dietary zinc. The specific response of these two physiological adjustments to changes in intake is discussed in greater detail later.

**Adjustments in fractional zinc absorption**

Since the methodology for the use of stable zinc isotopic tracers to study zinc metabolism was developed, there have been a number of studies of fractional zinc absorption in humans (Lee et al. 1993, Turnlund et al. 1982, 1986, Wada et al. 1985) (Table 1). All of the studies were performed with healthy adults who consumed diets with adequate amounts of zinc before implementation of the study diet. Four studies compared the response to different levels of zinc intake. When the zinc intake was reduced from 252 to 85 

μmol/d in a study of six men (Wada et al. 1985), fractional zinc absorption increased from 25 to 49%. In another study, when zinc intake was reduced from 192 to 63 μmol/d, fractional absorption increased from 44 to 63% (Lee et al. 1993). A study of a reduction to a very low intake (85–12 μmol/d) caused fractional zinc absorption to increase to 93% (Taylor et al. 1991). Doubling the zinc intake from 109 to 224 to 472 μmol/d caused fractional absorption to decline from 47 to 32 to 21%; the lower the intake of zinc, the higher the rate of fractional zinc absorption. Because fractional zinc absorption responds so dramatically to large changes in zinc intake, it is a gross indicator of the amount of zinc consumed. However, the fractional absorption of zinc varies sufficiently within a group of individuals fed the same amount of zinc that it becomes impossible to predict zinc intakes from the efficiency of absorption measured at a single time.

The increase in the efficiency of zinc absorption with reductions in intake allows more zinc to be absorbed than would have been the case had there been no change in the efficiency of absorption. However, the total amount absorbed is always less than the amount absorbed before the reduction in intake. For example, the increase in fractional zinc absorption from 40 to 93%, when dietary zinc was reduced from 85 to 12 μmol/d (Taylor et al. 1991), permitted 11 μmol of zinc to be absorbed rather than only 4.5 μmol if the fractional absorption had remained at 40%. This adjustment in the efficiency of zinc absorption provided an additional 6.5 μmol of zinc to the tissues.

When the zinc intake is very low, absorption occurs pri-
Adjustments in endogenous fecal zinc excretion

Although fractional zinc absorption increases dramatically when zinc intakes are reduced, the shift in EFZ excretion conserves more zinc for tissue use than does the change in zinc absorption. The overall adjustment in EFZ excretion may reflect a reduction in the amount of zinc secreted into the gut as well as an increased reabsorption of the endogenous zinc due to the up-regulation of the carrier-mediated process. For example, when the dietary zinc was reduced from 85 to 12 μmol/d (Taylor et al. 1991), EFZ dropped by 16 μmol/d. The up-regulation of zinc absorption conserved only 6.5 μmol/d. The larger decline in EFZ than that conserved by absorptive up-regulation of zinc absorption (Lee et al. 1993) (Fig. 3). After the men had been on the low zinc diet for 2 mo, fractional zinc absorption increased 48%, from 44 to 65%. Although fractional absorption increased, the total absorbed zinc declined from 85 to 41 μmol/d and endogenous fecal losses fell by 27%, from 65 to 48 μmol/d. During the 6 mo the men were on the low zinc diet, fractional and total zinc absorptions remained relatively constant, but the endogenous zinc losses continued to decline from 65 μmol/d during baseline to 48, 40 and 27 μmol/d at 2, 4 and 6 mo, respectively. After 6 mo, this reduction in EFZ losses allowed the men to achieve a positive crude zinc balance. Net crude balance was 4.7 μmol/d at 6 mo. It is unlikely, however, that this was sufficient to replace zinc losses in the integument and semen. Data from this study suggest that adjustments in zinc homeostasis with chronically low zinc intakes

The intake of most populations around the world falls below amounts considered to be adequate or desirable. The limited data available suggest that zinc homeostasis is maintained differently in those populations than occurs among individuals with adequate intakes. Rat studies show that EFZ losses are affected by the whole body zinc status as well as by current zinc intakes (Johnson et al. 1988). Fractional zinc absorption, on the other hand, is only influenced by current zinc intake. This suggests that the adjustment to a high zinc intake by a population in marginal zinc status due to a typical diet that is low in zinc would alter EFZ losses differently than if the high zinc diet were fed to a population in good zinc status.

A 6-mo study of low zinc intakes (63 μmol/d) in men confirmed the findings in rats, i.e., that EFZ losses are affected more by long-term poor zinc intakes than is fractional zinc absorption (Lee et al. 1993) (Fig. 3). After the men had been on the low zinc diet for 2 mo, fractional zinc absorption increased 48%, from 44 to 65%. Although fractional absorption increased, the total absorbed zinc declined from 85 to 41 μmol/d and endogenous fecal losses fell by 27%, from 65 to 48 μmol/d. During the 6 mo the men were on the low zinc diet, fractional and total zinc absorptions remained relatively constant, but the endogenous zinc losses continued to decline from 65 μmol/d during baseline to 48, 40 and 27 μmol/d at 2, 4 and 6 mo, respectively. After 6 mo, this reduction in EFZ losses allowed the men to achieve a positive crude zinc balance. Net crude balance was 4.7 μmol/d at 6 mo. It is unlikely, however, that this was sufficient to replace zinc losses in the integument and semen. Data from this study suggest that adjustments in zinc homeostasis with
very low intakes do not occur rapidly; however, changes continue to occur for months, possibly until equilibrium is eventually established.

The reduction in EFZ losses associated with the negative zinc balance may reflect a decrease in the size of rapidly turning over endogenous zinc pools. No functional consequences were reported associated with this loss of whole body zinc (Lee et al. 1993).

Another study of the homeostatic response to a chronic intake of diets low in zinc was performed in two groups of Chinese women: a group of rural women habitually consuming 5.2 mg zinc/d (80 μmol/d) and an urban group consuming 8.1 mg/d (125 μmol/d) (Sian et al. 1996). Although the urban women consumed ~35% more dietary zinc than the rural women, fractional zinc absorption did not differ between the two groups; the urban and rural women absorbed 34 and 31% of their intakes, respectively. Thus, the absolute amount of zinc absorbed by the urban women was higher than that of the rural women because they consumed more zinc: 42 versus 25 μmol/d. This increased amount of zinc absorbed by the urban women (17 μmol/d) was nearly balanced by the increased amount of endogenous zinc excreted in the feces: 15 μmol/d (i.e., 35 versus 20 μmol/d). Thus, the rural women, who were consuming only 80 μmol zinc/d, achieved homeostasis and zinc balance by reducing EFZ losses rather than changing the fractional rates of zinc absorption.

These two studies of low zinc intakes (Lee et al. 1993, Sian et al. 1996), as well as other studies performed in healthy, young infants (Krebs et al. 1993), show that the EFZ excretion is directly related to the total amount of zinc absorbed after individuals have established a state of equilibrium on the level of intake. If total zinc absorption is low, EFZ losses are also reduced. The quantity of zinc that is absorbed undoubtedly influences the amount of zinc in endogenous tissue pools, which in turn may be associated with the amount of endogenous zinc excreted in the feces.

In situations in which the tissue demand for zinc is high, as occurs during lactation, this relationship between true zinc absorption and EFZ losses is likely to change. Fractional zinc absorption increases during lactation (Fung et al. 1997) to provide additional zinc for milk synthesis. Endogenous fecal losses may be unchanged. Data from a study of fractional zinc absorption in a group of Amazonian women consuming low zinc diets support this hypothesis (Jackson et al. 1988). The women consumed only 129 μmol zinc/d before and during full lactation; fractional zinc absorption increased from 59 to 84%. The amount of zinc absorbed increased by 30 μmol/d, but the EFZ losses remained low to provide additional zinc for milk synthesis.

Renal adjustments with changes in dietary zinc

In comparison with the amount of zinc loss through the gastrointestinal tract, renal losses tend to be low, and they also remain constant over a wide range of intakes. Intestinal fecal losses vary by threefold, from 27 to 90 μmol/d, on intakes ranging from 63 to 472 μmol/d (Table 1); urinary losses range from 8 to 11 μmol/d. When zinc intake is very low, i.e., <50 μmol/d, urinary losses decline. Johnson et al. (1993) measured the changes in urinary zinc excretion when diets providing 21.9, 37.5, 51.6 and 67.8 μmol/d were fed. They found that urinary zinc excretion did not decline until zinc intake was reduced to <51.6 μmol/d.

The decline in urinary zinc occurs very rapidly, in 2–3 d after the initiation of a very low zinc intake (unpublished data). The urinary excretion data from a young man fed a diet providing only 4.5 μmol/d is shown in Figure 4. This decline in urinary zinc occurs before there are any changes in plasma zinc concentration or in fractional zinc absorption. The regulation of urinary zinc losses is not well understood. Studies in dogs showed that glucagon infusions increased urinary zinc without changing plasma zinc concentrations (Victory et al. 1981); this increase is inhibited by an infusion of insulin (Vander et al. 1983). These hormonal changes in urinary zinc excretion occurred without altering glomerular filtration rates. Also, there was no evidence that other cations were affected by glucagon or insulin infusions. Possibly, the shifts in urinary zinc excretion are mediated by adjustments in renal tubular zinc transport. Cysteine infusion has been shown to increase urinary zinc excretion dramatically by causing a rise in net tubular secretion (Abu-Hamdan et al. 1981).

The fall in EFZ conserves much more zinc than the changes in urinary zinc with an acute decrease in zinc intake. A reduction in dietary zinc from 85 to 12 μmol/d conserved ~16 μmol of endogenous fecal losses (Taylor et al. 1991), but only 2–6 μmol zinc/d was conserved by adjustments in renal excretion. Although the changes in urinary zinc occur quickly and may be as much as 100-fold, the amount of zinc excreted...
in the urine is much less than that excreted in the feces, so less is conserved. Because renal adjustments have a relatively small impact on zinc conservation, it seems logical that adjustments in renal conservation are not induced unless the intakes are extremely low.

The rapid changes in endogenous fecal and urinary zinc losses with low zinc diets limit the drop in plasma zinc concentrations (unpublished data) (Fig. 5). When dietary zinc was reduced from 241 to 4 μmol/d, fecal and urinary zinc losses dropped ~75% by the end of the second week, whereas the plasma zinc concentrations were unchanged. When dietary zinc intake was reduced from 252 to 85 μmol/d (Wada et al. 1985), fecal zinc losses declined markedly; there were no changes in plasma zinc concentrations. Plasma zinc concentrations change very slowly, if at all, with changes in zinc intake reducing the value of this measurement for assessing zinc status. Because the plasma must provide zinc to all of the tissues, maintaining relatively constant plasma zinc concentrations is essential to sustaining normal function and health.

Other sources of zinc loss

Additional zinc is lost daily in integumental losses (i.e., sweat and other surface losses), seminal emissions, menstrual losses and hair and nail growth. Whole body surface losses average ~7 μmol/d when zinc intake averages ~130 μmol/d (Milne et al. 1983). When zinc intakes were reduced to 55 μmol/d, surface losses declined by ~50%. Surface losses also tended to rise with high zinc intakes (518 μmol/d). These adjustments in surface losses occurred even though plasma zinc remained within the normal range. It is not known how this adjustment in integumental zinc losses is made with changes in intake.

Semen is rich in zinc and can represent a significant source of zinc loss with frequent ejaculations. One ejaculation contains ~ 9 μmol zinc. Semen zinc losses decline with zinc depletion; severe zinc depletion caused a 50% decrease in the amount of zinc per ejaculum (Baer and King 1984). This reduction in semen zinc seems to be due to a decrease in semen volume rather than a change in the concentration of zinc in the semen (Hunt and Johnson 1990).

Typical hair and nail growth account for only 0.5 μmol zinc loss/d (Baer and King 1984).

Shrink in tissue zinc concentrations to conserve whole body zinc

Zinc, the most abundant intracellular element, is found in all body tissues, with ~85% of the whole body zinc in muscle and bone (Table 2). Another 11% is found in the skin and liver. The remaining 2–3% of the whole body zinc is in all of the other tissues (Jackson 1989).

When the dietary zinc supply is very low or if a marginal intake is consumed for a long period of time, homeostatic adjustments may not be sufficient to replace zinc losses and a negative zinc balance occurs. With severe zinc deficiency, i.e., <0.06 μmol/g diet, the whole body zinc content of experimental animals decreased to ~30% of that of control animals (Jackson et al. 1982), but zinc loss was not uniform across all tissues. Hair, skin, heart and skeletal muscle zinc concentrations remained constant, whereas plasma, liver, bone and testes zinc concentrations dropped significantly. After the low zinc diet was fed for 80 d, plasma zinc was 45% lower than that of controls, testes zinc was 53% lower, bone zinc was 64% lower and liver zinc was 19% lower. It is interesting that hair zinc concentrations did not change in this study of experimental animals. Hair zinc has been used as a measure of zinc status in humans (Ambidge 1982). Possibly, hair zinc concentrations change with long-term, marginal intakes but not with severe depletion as was studied in these experimental animals.

A set of tissue zinc measurements from three patients in whom zinc metabolism was abnormal provides unique information about the effect of zinc depletion on tissue zinc concentrations in humans (Jackson et al. 1982). In one patient, hair and skeletal muscle samples were collected; in a second patient, skin and plasma samples were collected before death and tissue samples were removed postmortem. In the third patient, an 11-γ-old boy with thalassemia treated with a zinc chelating agent, liver, bone, testes, heart and quadriceps muscle were removed postmortem and analyzed for zinc. As was observed in experimental rats, hair, skin, skeletal muscle and heart zinc concentrations were unchanged in these patients, but bone, liver, testes and plasma zinc levels were significantly below normal values. Bone zinc was 1.68 μmol/g dry weight (normal range, 2.30–3.80 μmol/g dry weight). Liver zinc was 1.01 μmol/g dry weight (normal range, 1.24–3.34 μmol/g dry weight). Testes zinc was 0.49 μmol/g dry weight (normal range, 0.78–1.91 μmol/g dry weight), and plasma zinc ranged from 4.3 to 11.7 μmol/L (normal range, 11.4–17.8 μmol/L).

**TABLE 2**

*Distribution of zinc within the body in a normal adult man (70 kg)*

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Zn concentrate μg/g wet weight</th>
<th>Percent of total body zinc %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal muscle</td>
<td>51</td>
<td>57</td>
</tr>
<tr>
<td>Bone</td>
<td>100</td>
<td>29</td>
</tr>
<tr>
<td>Skin</td>
<td>32</td>
<td>6</td>
</tr>
<tr>
<td>Liver</td>
<td>58</td>
<td>5</td>
</tr>
<tr>
<td>Brain</td>
<td>11</td>
<td>1.5</td>
</tr>
<tr>
<td>Kidneys</td>
<td>55</td>
<td>0.7</td>
</tr>
<tr>
<td>Heart</td>
<td>23</td>
<td>0.4</td>
</tr>
<tr>
<td>Hair</td>
<td>150</td>
<td>~0.1</td>
</tr>
<tr>
<td>Blood plasma</td>
<td>1</td>
<td>~0.1</td>
</tr>
</tbody>
</table>

1 Adapted from Jackson 1989.
absorbed zinc passes through the plasma, i.e., adult, the plasma contains a tracer of zinc, $^{70}$Zn, we measured indices of zinc kinetics in five constant concentration. Using an intravenous stable isotopic label, the flux of zinc out of the plasma must be rapid to maintain a constant concentration. Over rates and avid retention of zinc released from selected tissues, such as muscle, and the release of that endogenous zinc for critical metabolic functions. The prevention of tissue catabolism by force feeding the animals seems to prevent a homeostatic response to an extremely low zinc diet, and survival is impaired.

Use of tissue zinc as a reserve in severe zinc depletion

The rapid onset of the clinical symptoms of zinc deficiency with severe depletion indicates that there is no store for zinc like there is for energy or iron. In all growing species that have been studied, a marked reduction in dietary zinc is invariably followed quickly by a reduction in food intake and growth failure (O’Dell and Reeves 1989). When weanling rats were force fed a zinc-deficient diet so that they were prevented from reducing their growth rates, the rats rapidly became ill and died. In contrast, rats fed similar diets ad libitum survive for several weeks longer, albeit with signs of zinc deficiency. They survived, however, at the expense of the use of their own tissue zinc. Typically, weanling animals fed zinc-deficient diets develop a cyclic pattern of food intake that is 3–4 d in length (O’Dell and Reeves 1989). This cyclic pattern in food intake causes the catabolism of tissues containing zinc, such as muscle, and the release of that endogenous zinc for critical metabolic functions. The prevention of tissue catabolism by force feeding the animals seems to prevent a homeostatic response to an extremely low zinc diet, and survival is impaired.

Zinc released from tissues during the catabolic phase is taken up and retained very efficiently by other tissues. This was demonstrated by Giugliano and Millward (1984). They measured the changes in weight and zinc concentrations in various organs after weanling rats had consumed a severely deficient diet for 24 d. During this period, the net gain in total body muscle zinc was $\sim 25 \mu$mol. This was only $\sim 5 \mu$mol more than the amount of zinc lost from bone during the same period. Accordingly, muscle tissue gained weight and maintained its zinc concentration by efficiently incorporating any zinc released by the bone and small amounts obtained from the diet. This avid retention of zinc in selected tissues during severe zinc deficiency contributes to the marked drop in endogenous zinc losses and the overall efficient use of dietary zinc.

Adjustments in gastrointestinal zinc absorption and intestinal endogenous zinc excretion are the primary means by which the body maintains constant tissue levels of zinc with varying intakes. With extremely low intakes or with prolonged marginal intakes, secondary homeostatic measures become operative. These secondary measures include a reduction in urinary zinc excretion, an increase in plasma fractional turnover rates and avid retention of zinc released from selected tissues, such as bone, in other tissues to maintain their zinc status.

LITERATURE CITED

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