Zinc homeostasis during lactation in a population with a low zinc intake[1–3]

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ABSTRACT

Background: There is a major increase in endogenous zinc excretion, specifically via the mammary gland, in early human lactation. Whereas fractional absorption of dietary zinc has been reported to increase in early human lactation, it is not known to what extent adaptive mechanisms may maintain zinc homeostasis, especially when dietary zinc intake is relatively low.

Objective: The objective of this study was to quantitate major variables of zinc homeostasis during early lactation in subjects from a population whose habitual dietary zinc intake is low.

Design: We studied 18 free-living lactating women from a rural community of northeast China whose infants were exclusively breast-fed. The subjects were studied at ≈2 mo of lactation with use of stable isotopes of zinc and metabolic collection techniques. Milk volume was measured with use of a deuterium enrichment method.

Results: The mean (±SD) secretion of zinc in milk was 2.01 ± 0.97 mg/d, the intake of zinc was 7.64 ± 1.61 mg/d, and the fractional absorption of zinc was 0.53 ± 0.09, for a total daily zinc absorption of 4.00 ± 0.71 mg/d. Endogenous zinc excretion in urine and feces was 0.30 ± 0.10 and 1.66 ± 0.97 mg/d, respectively.

Conclusions: Zinc balance, including zinc secreted in breast milk, was maintained at ≈2 mo of lactation in women whose habitual diet was low in zinc. Homeostasis was achieved by high fractional absorption of zinc and intestinal conservation of endogenous fecal zinc. *Am J Clin Nutr* 2002;75:99–103.

KEY WORDS Stable isotopes, absorption, excretion, homeostasis, endogenous zinc, milk zinc, lactation, zinc intake, China

INTRODUCTION

Quantitative information on zinc homeostasis under a wide range of environmental, especially dietary, and host circumstances is an essential prerequisite to a better understanding of dietary zinc requirements and of the circumstances that contribute to zinc deficiency. Populations that have what is apparently a habitually low or marginal dietary zinc intake can provide invaluable information on long-term homeostatic responses to these relatively low intakes. The advent and progressive refinement of zinc stable-isotope techniques have facilitated the acquisition of data on key variables of zinc homeostasis, even in populations located in remote, rural regions (1).

See corresponding editorial on page 2.

One recent example of such a study by this collaborative group was undertaken in rural northeast China (2). The subjects were young women who had never been pregnant and whose habitual dietary zinc intake was low, ≈5 mg/d. However, the phytate intake of this population, for whom milled wheat and rice are the major food staples, is also low, indicating moderate to good bioavailability of dietary zinc (3) and other minerals. These subjects maintained positive net absorption by intestinal conservation of endogenous zinc (2).

The present study was undertaken to determine to what extent and by what homeostatic mechanisms zinc balance could be maintained at a time of increased physiologic zinc requirements in this population. We elected to study women at ≈6–8 wk of lactation when zinc output by the mammary gland is still relatively high (≈2 mg Zn/d; 4, 5) and at which stage postpartum any release of zinc from the involuting uterus is complete (3).

SUBJECTS AND METHODS

Study design

This was a cross-sectional study of free-living, healthy, lactating women toward the end of their second month of lactation who continued to consume their habitual diet in their homes throughout the study. Zinc stable-isotope techniques (6) were used in combination with measurements of total zinc and careful metabolic collections. Milk output was measured with a deuterium enrichment method (7). Key variables of zinc homeostasis that were measured directly with these techniques included dietary zinc, fractional zinc absorption (8), endogenous fecal zinc (6), milk zinc concentration, and 24-h urinary zinc excretion.

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[2] Supported by Mead Johnson Nutritionals, Proctor&Gamble, and The Colorado Clinical Nutrition Research Center (P30-DK 48520).

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Received March 20, 2001.

Accepted for publication July 20, 2001.

Variables of zinc homeostasis that were calculated from these data included total zinc absorption (mg/d), net (apparent) zinc absorption, milk zinc output (mg/d), and zinc retention (mg/d). Data were evaluated in terms of zinc homeostasis and balance and were compared with corresponding data from a study conducted 4 y earlier in the same population that targeted young women who had never been pregnant (2).

Investigative team

Thirteen caseworkers from the Miyun County Woman and Child Health Care Institute were trained to assist 3 of the authors (LS, LF, and JEW) with the study. Each caseworker was assigned to 1 or 2 subjects and assisted with isotope administration and with the collection of and storage of data and samples.

Subjects

Eighteen lactating women (1–2 mo postpartum) who were exclusively breast-feeding their infants were recruited from 5 villages of Xitiankezhuang town, Miyun County, which is located ≈100 km northeast of Beijing. The distance between these villages is ≤4 km. These sites are mountainous, and the types of food consumed, social conditions, and average income of the villages were similar. The site of the study was 20 km from the site of the previous study (2). Both studies were conducted in January, and food patterns, ecologic environment, and climate had not changed over the previous 4 y. Neither the subjects nor their infants had any evidence of either acute or chronic disease. Subjects did not smoke, did not drink alcohol, and did not take multivitamin or mineral supplements. This study did not include a control group; however, selected data were compared with recent data for never-pregnant women from the same population (2). The Academic Committee of Beijing Children's Hospital provided ethical approval for the study.

Dietary intake

After careful instruction, each subject completed a 3-d diet record before the metabolic studies began. These records were analyzed by using tables of Chinese foods prepared by the Chinese Academy of Preventive Medicine (9). Phytate intake was calculated by using the food phytate content from the previous study in the same area (10). The kinds of foods consumed by the subjects were similar to those consumed by young, never-pregnant women in the same geographic area, except that the subjects consumed more eggs and more staple foods. Subjects continued to consume this habitual diet during the study period.

Isotope preparation and administration

Enriched zinc stable isotopes (^{67}Zn and ^{70}Zn) were obtained as the oxide (Oak Ridge National Laboratory, Oak Ridge, TN). Enriched deuterium oxide (99.9%) was obtained from Cambridge Isotope Laboratories (Andover, MA). Zinc isotopes were dissolved in 0.5 mol H_2SO_4/L to prepare a stock solution. For preparation of orally administered doses, the stock solution of enriched ^{67}Zn was diluted with triply deionized water and then adjusted to pH 5.0 with ammonium hydroxide. This solution was filtered through a 0.2-μm filter to remove pyrogens. Sterile techniques were used to prepare doses from the stock solution of ^{70}Zn for intravenous administration. The pH was adjusted to 6.0 with ammonium hydroxide and the stock solution was diluted with sterile isotonic sodium chloride to a concentration of 1.5 mmol enriched ^{70}Zn/L. The solution was filtered as was the oral preparation. Zinc concentrations were determined by atomic absorption spectrophotometry and were adjusted for the different atomic weights of each preparation. The solutions were tested to ensure that they were pyrogen free.

An accurately weighed quantity of ^{70}Zn (≈0.38 mg) was administered intravenously over 5 min via the peripheral forearm vein. Accurately weighed quantities of ^{67}Zn were administered with water at the midpoint of each of the 3 main meals of the day. The total administered dose (≈1.9 mg) was divided in proportion to the total zinc content of each meal. Accurately weighed quantities of deuterium oxide (≈5.5 g) were administered orally to mothers in the morning. The containers for ^{67}Zn and deuterium were carefully rinsed 3 times with water and this water was also consumed. Isotopes were administered by an experienced nurse, who was supervised by 2 of the authors (LS and JEW). Brilliant blue was administered as a visible fecal marker 7 d after isotope administration and then exactly 120 h later (day 12).

Sample collection

Baseline fecal and urine samples were collected before isotope administration. Individual fecal samples were collected separately and quantitatively in plastic bags until 10–13 d after isotope administration; the collection was complete with passage of the second fecal marker. Twenty-four–hour urine samples were collected from 3 through 12 d after isotope administration. Acid-washed plastic containers were used for the collections. In the 5 d between administration of the 2 fecal markers, duplicate meals were collected in acid-washed plastic bottles. Milk samples were collected by hand expression after the nipple and areola were cleaned with deionized water and dried; a midfeeding sample was obtained from one breast. About 5 mL breast milk and 0.2 mL saliva from the infants were collected 1 d before and 1, 2, 3, 13, and 14 d after the study (11). Breast-milk samples were collected in zinc-free vials. All samples were transported to the local hospital within 2 h for storage at −20°C.

Sample preparation and analyses

Accurately weighed aliquots of homogenized feces and 150-mL aliquots of individual urine samples were dried in an electric oven before being ashed in a muffle furnace at 450°C (12). Ashed fecal samples and ashed urine samples were reconstituted quantitatively in 10 mL of 6 mol HCl/L and in ≈40 mL of 6 mol HCl/L, respectively. The total zinc concentration in these reconstituted fecal samples was measured with a flame atomic absorption spectrophotometer fitted with a deuterium-arc background correction lamp (model 2380; Perkin-Elmer Corporation, Norwalk, CT). Zinc in ashed fecal and urine samples was separated from other inorganic constituents by ion-exchange chromatography. Zinc isotopic ratios were determined by fast atom bombardment–induced secondary ion mass spectrometry on a double-focusing mass spectrometer (model VG 7070E HF; Fisons-VG Analytic, Manchester, United Kingdom) equipped with an atom gun (Ion Tech, London). The mass spectrometer was operated at low resolution, and polyatomic isobaric interferences were eliminated by using secondary ion energy selection. The overall CV for the precision of this technique was 1.5%.

Hydrogen in the water from saliva and breast-milk samples was reduced to hydrogen gas by using a standard zinc reduction

TABLE 1
Profile of mothers and infants[1]

	Mothers (n = 18)	Infants (n = 18)
Age	26 ± 2 y	48 ± 11 d
Weight (kg)	60 ± 7	5.35 ± 0.81
Height (cm)	157 ± 4	56.3 ± 2.8
Birth weight (kg)		3.29 ± 0.46
Energy (kJ/d)	9330 ± 1926	—
Protein (g/d)	73 ± 16	—
Fat (g/d)	39 ± 22	—
Carbohydrate (g/d)	405 ± 95	—
Calcium (mg/d)	284 ± 130	—
Zinc (mg/d)	7.8 ± 1.7	—
Iron (mg/d)	12.2 ± 4.1	—
Copper (mg/d)	1.8 ± 0.6	—
Selenium (μg/d)	72.6 ± 20.6	—
Phytic acid (mg/d)	923 ± 252	—

[1] $\bar{x}$ ± SD. Intakes from 3-d diet records.

process (13). All samples were prepared in duplicate. Pyrex glass reaction vessels (Ace Glass Inc, Vineland, NJ) containing Hayes zinc (Biogeochemical Laboratories, University of Indiana, Bloomington) were evacuated to 10^{-2} Pa and then filled with nitrogen. A 2-μL sample (saliva or centrifuged breast milk) was placed into a small (6-mm internal diameter and 40-mm length) glass vial with a tapered end. This vial was then quickly placed in a nitrogen-filled reaction vessel. The sample was frozen with the use of liquid nitrogen. Next, the vessel was reevacuated to 10^{-2} Pa, sealed, removed from the vacuum, placed in a heating block (Dri-Block DB-4; Techne, Cambridge, United Kingdom), and heated to 500°C for 30 min. After being heated, the reaction vessels were attached to a dual-inlet isotope ratio mass spectrometer (VG Optima; Micromass, Manchester, United Kingdom) for the measurement of deuterium enrichment (14). After calibration, the samples were analyzed in duplicate with the use of a laboratory hydrogen standard as reference. The hydrogen standard was referenced to Vienna Standard Mean Ocean Water (VSMOW) and the results were corrected for H_3^+ generation. The SD of concurrent analyses of reference water samples was 2.9 δ (n = 25).

Food samples were accurately weighed and homogenized. The homogenized food samples and individual breast-milk samples were dried and ashed. The zinc concentration was determined as it was for the fecal sample.

Data processing

Isotopic enrichments were calculated from measured isotopic ratios by using an established method to correct for the presence of the other isotopic label. For each particular isotope label used, enrichment is defined as all zinc in the sample from an isotopically enriched source divided by the total amount of zinc in the sample.

Fractional absorption was measured by using a dual-isotope urine enrichment method (8). The mean fractional absorption for independent daily measurements from days 3 to 12 of the metabolic studies was determined. The mean relative SD was 13% (n = 18). Endogenous fecal zinc excretion was measured with the use of an isotope-dilution technique (6):

$$\text{Endogenous fecal zinc (mg/d)} = \Sigma(F_i \times f_i)/(u \times d) \qquad (1)$$

where F_i is the quantity of zinc (mg) in each individual fecal sample collected between the appearance of the visible markers, f_i is the enrichment of intravenously administered isotope (^{70}Zn) in each of these samples, u is the average ^{70}Zn enrichment in urine between administration of the 2 visible markers, and d is the duration (days) of the collection period (ie, 5.0 d).

Total zinc absorption was calculated by multiplying the mean dietary zinc intake (mg) derived from the 5-d duplicate food collection by the fractional absorption of the extrinsic label. Net (apparent) zinc absorption was calculated as the difference between total zinc absorption and endogenous fecal zinc. Net zinc absorption was also calculated by subtracting total fecal zinc from dietary zinc.

Breast-milk output was determined by using the 2-compartment model and by calculating algorithms described by Coward (7). Infant total body water was estimated by averaging the total body water values predicted from subject weight, height, or age in 3 population studies (15–17). The deuterium enrichment data from isotope ratio mass spectrometer measurements of breast milk and saliva were converted to tracer/tracee values, and initial estimates were derived by nonlinear regression with the use of GRAPHPAD PRISM (version 3.00 for WINDOWS; GraphPad Software Inc, San Diego). Final variable estimates were determined by using WINSAAM (18, 19) and took into account the precision of individual enrichment data. Secretion of zinc in milk for each subject was calculated by multiplying the individual mean milk zinc concentration (mg/L) by the individual milk output (L/d).

Statistical analysis

Results are expressed as means ± SDs, except in Figure 1, in which the results are given as means ± SEs. Pearson's correlation coefficients were determined.

RESULTS

The ages, weights, and heights of lactating women and their infants are given in **Table 1**. Intakes of selected nutrients, calculated from 3-d records, are also included in Table 1. About 13% of energy was from protein, 15% was from fat, and 72% was from carbohydrate.

The fractional absorption of zinc was 0.53 ± 0.09 and the zinc intake was 7.64 ± 1.61 mg/d. Thus, total zinc absorption was 4.00 ± 0.71 mg/d (**Figure 1**). Endogenous zinc excretion was 1.66 ± 0.97 and 0.30 ± 0.10 mg/d in feces and urine, respectively.

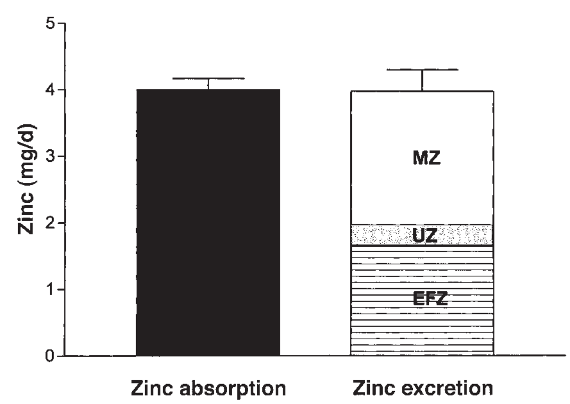

FIGURE 1. Mean (±SE) total zinc absorption and zinc excretion, including endogenous fecal zinc excretion (EFZ), urinary zinc excretion (UZ), and milk zinc secretion (MZ).

The American Journal of Clinical Nutrition

TABLE 2
Comparison of key variables of zinc homeostasis between lactating and never-pregnant women[1]

Zinc	Lactating women (n = 18)	Never-pregnant women[2] (n = 10)
Dietary intake (mg/d)	7.6 ± 1.6	5.2 ± 0.2
Fractional absorption	0.53 ± 0.09	0.31 ± 0.03
Total absorption (mg/d)	4.00 ± 0.71	1.63 ± 0.23
Endogenous fecal excretion (mg/d)	1.66 ± 0.97	1.30 ± 0.07

[1] $\bar{x}$ ± SD.
[2] Data from reference 2.

Crude zinc balance calculated from these data (zinc absorption − endogenous fecal zinc − urinary zinc) was 2.04 ± 1.02 mg/d. Crude zinc balance determined from the nontracer metabolic balance data (dietary zinc − total fecal zinc − urine zinc) was 2.16 ± 1.59 mg/d.

The mean breast-milk zinc concentration was 2.34 ± 0.83 mg/L and milk output was 0.85 ± 0.21 L. The milk zinc output was 2.01 ± 0.97 L/d. The total endogenous zinc loss, including that secreted via the mammary gland, was 3.97 ± 1.36 mg/d (Figure 1). Zinc balance adjusted for secretion via the mammary gland was 0.02 L/d. No significant correlation was found between any of the following variables of zinc homeostasis: zinc intake, total zinc absorption, endogenous fecal zinc, net zinc absorption, urinary zinc, and milk zinc output.

DISCUSSION

The present study was conducted in a population from the same rural area of northeast China as in our previous study; both populations had low dietary zinc intakes (2). No social, economic, or dietary changes had occurred in this population in the 4-y interval since the earlier study. Because these lactating women had higher intakes of staple foods and eggs than did an age-matched sample of never-pregnant women from the same region, the lactating women had 84% higher energy, 139% higher protein, and 50% higher zinc intakes. The higher zinc intake was one reason why zinc homeostasis was maintained throughout the study (**Table 2**). A second and greater reason was that fractional zinc absorption was 71% higher in the lactating women than in the never-pregnant women. These 2 factors combined resulted in a total zinc absorption that was 2.37 mg/d higher in the lactating than in the never-pregnant women, ie, a sufficiently higher value that more than balanced the zinc output by the mammary gland in the lactating women. An increase in fractional zinc absorption during lactation was reported previously in South America (20) and in North America (21, 22). The large differences in actual fractional zinc absorption between the different studies of lactating women are likely attributable in part to differences in habitual intakes of bioavailable zinc. Methodologic differences, however, may also be a factor.

This increase in fractional zinc absorption occurred despite a higher zinc intake. Typically, there is a strong inverse relation between the amount of zinc ingested (assuming similar bioavailability) and the fractional absorption of this mineral (23). Indeed, it is unclear whether factors other than zinc intake and bioavailability influence fractional absorption. These and other data from lactating women provide convincing evidence that, at least under this special physiologic circumstance, humans can regulate the fraction or the total amount of zinc absorbed in response to signals other than the quantity of ingested zinc that is potentially available for absorption.

In the never-pregnant women with a habitually meager zinc intake in our previous study (2), zinc homeostasis was maintained via intestinal conservation of endogenous zinc (2). Superficially, it might appear that intestinal conservation of endogenous zinc had no greater role, or even a slightly reduced role, in maintaining zinc homeostasis during the peak demands of lactation (Table 2). However, there is typically a strong correlation between the quantity of zinc absorbed and the quantity of endogenous zinc excreted via the intestine (2, 24, 25). This relation leads to the conclusion that the extent to which the intestine is conserving zinc can be evaluated adequately and appropriately only when it is examined in relation to the quantity of zinc absorbed (24, 25). When the mean excretion of endogenous zinc in the feces of these lactating women was examined on a plot of the linear regression of endogenous fecal zinc versus total zinc absorption for the never-pregnant Chinese women (2), it was observed to be below the lower 95% CI (**Figure 2**). This suggests that intestinal conservation of endogenous zinc was more efficient during high zinc output from the mammary gland in the lactating women than in the never-pregnant women. At a total zinc absorption that is 2.4 mg/d higher in the lactating women than in the never-pregnant women, the anticipated corresponding increase in endogenous fecal zinc would be ≈1.5 mg Zn/d according to Figure 2. In fact, endogenous fecal zinc excretion was a mere 0.36-mg/d greater in the lactating women than in the never-pregnant women.

These calculations indicate that intestinal conservation of endogenous zinc is a major factor in achieving zinc balance early in lactation in a population of women whose habitual dietary zinc is low. Moreover, although the daily fecal excretion rate of endogenous zinc was slightly higher in the lactating women in the present study, this conservation of zinc was greater than in the never-pregnant women studied previously (2) when evaluated in relation to absorption. More specifically, a reasonable interpretation of these data, based on the calculations outlined in the previous paragraphs, is that intestinal conservation of endogenous zinc contributed ≈50% to the adaptation of regulation of zinc metabolism in the gastrointestinal tract in early lactation. This is in

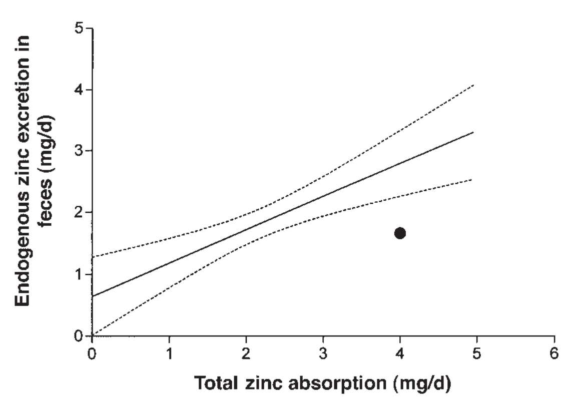

FIGURE 2. Linear regression and 95% CIs (dashed lines) of endogenous zinc excretion in feces (EFZ) versus total daily zinc absorption in the never-pregnant women. The black dot indicates the mean value of EFZ for lactating women in the same geographic area.

The American Journal of Clinical Nutrition

addition to the background adaptation to the low zinc intake in the never-pregnant women (2), which appears to be attributable entirely to conservation of intestinal endogenous zinc.

Urinary zinc excretion was reported to be lower during lactation than during nonlactation in one study (26). The rate of urinary zinc excretion in the lactating subjects included in that study was, however, similar to that for the nonlactating subjects in the earlier study. Moreover, the potential for conserving endogenous zinc by reducing renal excretion is limited.

Another aspect of these results that merits attention is their nutritional and public health implications. The zinc intake of the study population is at the lower end of the spectrum of reported zinc intakes worldwide (27). Despite the higher overall food consumption during lactation (≈50%), the zinc intake of this population was substantially lower than, for example, reported zinc intakes of lactating women in North America (4, 25, 28). Despite the low zinc intake of the present study population, it is concluded that zinc homeostasis is effectively maintained by an increase in zinc intake and by adaptations in the regulation of zinc metabolism in the gastrointestinal tract. The present study did not include any biomarkers of zinc status, but the breast-milk zinc concentrations in this population indicate that the supply of zinc to the breast-fed infant was not compromised to any measurable extent by the low maternal zinc intakes. We conclude that, although homeostatic mechanisms may have been stretched to respond effectively to a physiologic state of increased zinc requirements, the capacity of these mechanisms was adequate to maintain zinc homeostasis and balance.

The mean molar ratio of phytate to zinc in the diet of these subjects was calculated to be 11.7 ± 2.9 and, although this ratio is not high, it was in a range that might be expected to have some inhibitory effect on zinc absorption (29, 30). It is unknown whether individuals whose habitual diets are characterized by high phytate intakes and high molar ratios of phytate to zinc could adapt so effectively to maintain zinc homeostasis during lactation.

In conclusion, zinc homeostasis and balance were maintained by women at a stage of lactation in which the zinc output in milk was relatively high despite a habitually low dietary intake of this micronutrient. Zinc homeostasis and balance were achieved because of a high total zinc absorption (mainly attributable to a high fractional zinc absorption) and intestinal conservation of endogenous zinc relative to this high absorption.

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