Compartmental Model of Zinc Metabolism in Healthy Women

N.M. LOWE,† D.M. SHAMES,‡ L.R. WOODHOUSE,† J.S. MATEL,† AND J.C. KING§
†Department of Nutritional Sciences, University of California at Berkeley, CA 94720. ‡Department of Radiology, University of California at San Francisco, CA 94143, and §USDA Western Human Nutrition Research Center, San Francisco, CA 94129, USA

Keywords zinc, stable isotopes, tracer kinetics, compartmental model

Compartmental analysis of tracer kinetics has provided valuable insights into the metabolism of many nutrients, including trace minerals. Using radioactive isotopes a detailed compartmental model of zinc metabolism was developed in humans (Wastney et al. 1986). Stable isotopes provide more limited information, but are useful for populations where radioactive tracers are discouraged. Our research group is interested in defining the mechanisms regulating zinc homeostasis in pregnant and lactating women. Thus, we developed a simple model of zinc metabolism in young women, using stable isotopes of zinc, that can be used in the future to define the relationship between zinc status and homeostasis in pregnant women.

Materials and Methods

Subjects: Six women, aged 30 ± 11 years (mean ± SD), were recruited for the study. All of the women were Caucasian and none had acute or chronic health problems. The weight of the women averaged 54.2 ± 8.9 kg, and their body mass index was 20.7 ± 2.6 kg/m². The usual dietary zinc intakes of this group, assessed prior to the study with 3-d weighed food intake records, averaged 8.3 ± 3.4 mg/d. The experimental design was approved by the University of California at Berkeley Committee for the Protection of Human Subjects. All participants gave written, informed consent.

Experimental Design: Subjects were maintained on a constant diet containing 7.0 ± 0.1 mg Zn/d for a 7-d equilibration period prior to tracer administration. On the morning of day 8 an indwelling catheter was placed in an arm vein and a fasting blood sample (8 mL) taken in a heparinized zinc-free polypropylene syringe (“Monovet”, Sarstedt, Hayward, CA). Fifteen minutes after consuming a breakfast meal containing 1 mg zinc, each subject drank 213 g orange juice containing 1.3 mg of the oral tracer 67Zn (enriched to 91.8% abundance; Cambridge Isotope Laboratories, Woburn, MA). Immediately thereafter, 0.4 mg of a second tracer, 70Zn (enriched to 85.03% abundance; Oakridge National Laboratory, Oak Ridge, TN), was administered intravenously in the arm opposite to that used for sampling. Blood samples (8 mL) were taken via the catheter at timed intervals during the 7 h immediately post 70Zn administration, and daily for the next 7 d. The constant diet was continued for this 7-d period. All urinary and fecal output was collected for 7 and 11 d following tracer administration, respectively. All plasma, urine and fecal samples were stored at —20° until analysis.

Sample Preparation and Analysis: Total zinc concentrations of plasma, urine and fecal samples were measured using atomic absorption spectroscopy (AAS) (Smith-Hieftje-22, Thermo Jarrell Ash, Franklin, MA). Zinc isotope ratios were determined using inductively coupled plasma mass spectrometry (ICP-MS). For mass spectrometer analysis, plasma samples (3–4 mL) and fecal samples (0.3–0.5 g) were wet ashed in 5 mL concentrated HNO3 by microwave digestion, and inorganic salts were removed from urine samples using a chelating resin (Chelex 100 resin, 100–200 mesh, sodium form, Bio-Rad Laboratories, Hercules, CA). Zinc was purified from the mineral solutions using ion exchange chromatography (Type AG1X-8,

BioRad Laboratories). All acids used for the preparation of samples for ICP-MS were ultrapure (HCl: Optima brand, Fisher Scientific, Pittsburg, PA; HNO₃: Seastar brand, Seastar Chemicals Inc., Seattle, WA). Zinc isotope ratios were measured using a Perkin-Elmer Sciex ELAN 500 inductively coupled plasma mass spectrometer (Perkin-Elmer, Norwalk, CT). The data acquisition parameters were described previously (Roehl et al. 1995).

**Kinetic Analysis:** Stable isotope enrichment and total zinc mass in the plasma, urine and feces were analysed concurrently using SAAM/CONSAM (Berman and Weiss 1978). The model was numerically identified in each subject by using least squares parameter estimation.

**Results and Discussion**

The model developed to describe the isotope kinetics and steady state data is shown in Figure 1, along with the average values for the rate constants and compartment masses calculated for this subject group. The model fits the data from each subject well and has the least number of compartments required to account for the dynamic properties of our data and to remain consistent with known physiology. A linear array of three compartments was used to describe the gastrointestinal (GI) tract, compartment 4 corresponding to the stomach, compartment 5 the intestine and compartment 6 the colon. Compartment 1 is the plasma. It exchanges bi-directionally with the intestine (absorption and endogenous secretion). The fractional absorption of zinc (FZA), given by the ratio of $k_{1,5}$ to the sum of $k_{1,5}$ and $k_{6,5}$, was $0.28 \pm 0.04$ (MEAN ± SEM). The rates of endogenous secretion (Mass of compartment 1 x $k_{5,1}$) and excretion [(Mass of compartment 1 x $k_{5,1}$) x (1 - FA)] were $2.8 \pm 0.5$ mg/d and $2.0 \pm 0.3$ mg/d, respectively. The sum of the masses of the compartments that exchange rapidly with the plasma (compartments 1-3 and 5) are referred to as the exchangeable zinc pool (EZP). Those compartments may be a measure of zinc status.

![Figure 1. The circles indicate compartments representing kinetically distinct pools of zinc. The compartments are identified by numbers given at the top of each circle; the lower number is the compartment mass (mg). The arrows between the compartments represent the parameters, $k_{ij}$ (/day), i.e., the transfer rate constants of zinc form compartment j to compartment i. The rate constants and compartment masses represent the mean ± SEM for the six subjects.](image-url)
The EZP averaged 89 mg in these six women, which is estimated to be about 8% of total body zinc. There was a significant negative correlation (r = 0.69) between FZA and EZP when EZP is expressed on a per kg body weight basis. This inverse relationship suggests that the EZP may play a role in the homeostatic mechanisms that determine the proportion of dietary zinc absorbed. We are currently applying this compartmental modeling technique to data from a human zinc depletion-repletion study to more fully describe the relationship between Zn status, absorption and gastro-intestinal secretion.

Literature Cited


