Use of Zinc Stable Isotopes to Inform DRI Process for Infants & Children

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DRI Research Recommendations
- Biomarkers of Zn status
- Quantitative data on human Zn homeostasis under wide range of dietary conditions & at all ages
  - Using stable isotope methodology
  - Quantification of response to changes in intake & absorption
  - Studies should be long-term

Outline
- Review of stable isotope methodologies for zinc (dosing, collections, data)
- Issues particular to infants & young children (invasiveness, collections, constraints on study design)
- Considerations for refining estimates of Zn requirements and DRI’s
Rapidly Exchanging Zn Pools (~10%)

Intestine

Slowly Exchanging Pools

Endogenous Zn

Ingested Zn

Fractional Absorption

[Measurable by Stable Isotopes]

Unabsorbed diet Zn

Fecal Zn

Studies of Zn Homeostasis in Children

- Unable to conduct depletion/repletion studies
  - Need studies over wide range of intake
  - Use data from outside U.S.
- Factorial approach → physiologic requirement
- Absorbed Zn: entire day vs single (“test”) meal
  - “Absorption efficiency” of limited value

Stable Isotope Methodological Considerations

Presentation: Dr. Nancy Krebs
Studiedes of Zn Homeostasis in Infants:
“Historical” Considerations

- Metabolic collections:
  - Urine (uncontaminated, 100-120 ml/sample x 2/d)
  - Fecal (complete) x 7 d

- Dietary intake:
  - Test weights x 3 d
  - (Weighed diet records)


Stable Isotope Methodologies:
Advances Relevant to Children

- Urine measurement of fractional absorption (DITR)
  - Multiple measurements to average
  - “Spot” urines (10 ml)
  - 3 isotopes → fractional absorption w/ different conditions, same person
  - Requires IV dose

- Fecal monitoring w/ *Zn + rare earth element
  - Dysprosium: movement through GI tract tracks with Zn; not absorbed
  - Monitor completeness of fecal collections
  - Fractional absorption with partial fecal collections w/o IV dose

- Endogenous fecal Zn excretion
  - Isotope dilution method (not “balance” data)
  - Isotopes + daily dysprosium dosing
  - Partial fecal & spot urine collections x 4-5 days

- Better instrumentation → lower doses
  - Oral doses ≤ 10% of intake; IV doses less

- Cost of isotopes: ↓↓
  - (70Zn: $400/mg → $50/mg)

Presentation: Dr. Nancy Krebs
Advances in Understanding of Zn Homeostasis & Requirements for Children

Factors that affect FAZ & AZ:
- Amount of Zn in meal
- NOT: host Zn “status”
- Absorbed Zn = important!

Extension to “Saturation Response Model”

Mean Diet vs Absorbed Zn – DRI Adult Males: Saturation Response Model

Presentation: Dr. Nancy Krebs
Zn Intake vs Absorbed Zn in Infants (2-4 mo):
Saturation Response Model

Absorbed Zn vs Endogenous Fecal Zn:
Breast Fed & Formula Fed Infants

Absorbed Zn vs Zn Intake at 7 mo:
Implications for Complementary Foods for
Breastfed Infants

Presentation: Dr. Nancy Krebs
Peruvian Pre-school Children: Zn-fortified Wheat Study

- 3 levels of Zn Fortification (0, 3, 9 mg/100 g)
- 3 meals/d, absorption studies x 2 (BL + 50 days)
- Low Plasma Zn at BL ~ 20%
- No treatment x time effect

Lopez de Romana, et al, 2004

Chinese Toddlers (23 mo): Dietary Zn Intake vs Absorbed Zn

- Mean diet Zn: 1.9 mg/d
- FAZ: 0.35
- Abs Zn: 0.63 mg/d
- Endog Fecal Zn: 0.67 mg/d
  (> FNB est. ~ 34 ug/kg/d)
- Mean Plasma Zn: 65 ug/dL (48% < cut-off)
- Conclude: Sub-optimal intake; homeostasis ≠ compensate; Zn deficient

Sheng, AJCN, 2006 (in press)

Effects of Phytate on Zn Absorption

Trivariate model of Zn absorption as a function of dietary Zn and phytate
Selected prediction curves for constant phytate:Zn molar ratios

Presentation: Dr. Nancy Krebs
UL for Zinc for Infants & Young Children

Summary of Process for Determining UL:
- Hazard Identification
- Dose-Response Assessment
- Intake Assessment
- Risk Characterization

UL vs. Distribution of Intake* (Infants 7-12 mos)

* DRI, pp 672-673

Presentation: Dr. Nancy Krebs
Conclusions - I

UL for Zn for infants & young children:
- Is routinely exceeded, largely due to formula and food fortification
- No evidence of adverse effects
- Should be amended [asap!]

Conclusions - II

- Advances in stable isotope methodology have enabled studies in diverse pediatric populations and settings
- Application of stable isotopes to studies of Zn homeostasis in infants & children suggest:
  - Absorption characterized by saturation response model
  - Most important factors influencing Zn absorption = quantity of Zn ingested + phytate
  - Homeostatic responses insufficient to prevent deficiency
  - Comparison of population intake to current EAR predicts response to interventions; need to relate to intervention trials & functional outcomes

Acknowledgements:
K. Michael Hambidge
Leland V. Miller
Jamie Westcott
Lei Sian
Xiaoyang Sheng

[Photo by LV Miller]