A dynamic model for predicting growth in zinc-deficient stunted infants given supplemental zinc

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ABSTRACT

Background: Zinc deficiency limits infant growth and increases susceptibility to infections, which further compromises growth. Zinc supplementation improves the growth of zinc-deficient stunted infants, but the amount, frequency, and duration of zinc supplementation required to restore growth in an individual child is unknown. A dynamic model of zinc metabolism that predicts changes in weight and length of zinc-deficient, stunted infants with dietary zinc would be useful to define effective zinc supplementation regimens.

Objective: The aims of this study were to develop a dynamic model for zinc metabolism in stunted, zinc-deficient infants and to use that model to predict the growth response when those infants are given zinc supplements.

Design: A model of zinc metabolism was developed using data on zinc kinetics, tissue zinc, and growth requirements for healthy 9-mo-old infants. The kinetic model was converted to a dynamic model by replacing the rate constants for zinc absorption and excretion with functions for these processes that change with zinc intake. Predictions of the dynamic model, parameterized for zinc-deficient, stunted infants, were compared with the results of 5 published zinc intervention trials. The model was then used to predict the results for zinc supplementation regimes that varied in the amount, frequency, and duration of zinc dosing.

Results: Model predictions agreed with published changes in plasma zinc after zinc supplementation. Predictions of weight and length agreed with 2 studies, but overpredicted values from a third study in which other nutrient deficiencies may have been growth limiting; the model predicted that zinc absorption was impaired in that study.

Conclusions: The model suggests that frequent, smaller doses (5–10 mg Zn/d) are more effective for increasing growth in stunted, zinc-deficient 9-mo-old infants than are larger, less-frequent doses. The dose amount affects the duration of dosing necessary to restore and maintain plasma zinc concentration and growth.


Keywords: growth, infants, model, simulation, zinc

INTRODUCTION

Zinc deficiency, which affects ~25% of the global population, is one of the most prevalent nutritional problems (1). It is a primary cause of poor growth and development in children (2). Zinc deficiency can arise from insufficient zinc intake, poor zinc absorption, or excessive zinc losses (3). A meta-analysis of 55 studies reported that zinc supplementation significantly increased weight and linear growth, reduced the incidence of diarrhea by 20%, lowered respiratory infections by ~15%, and decreased mortality in infants >1 y of age by 18% (4). The WHO recommends the use of multiple micronutrient powders containing zinc for home fortification of complementary foods consumed by infants 6–23 mo old in nutritionally vulnerable populations (5, 6).

Zinc supplementation programs recommend criteria for identifying target populations and effective strategies for zinc delivery (7). A WHO/UNICEF/International Atomic Energy Agency/International Zinc Nutrition Consultative Group interagency group recommended that populations at risk of zinc deficiency can be determined by the prevalence of low zinc intakes, low serum zinc concentrations, or a low height-for-age (i.e., stunting) (8). Serum zinc concentrations alone should not be used to diagnose zinc deficiency because serum zinc concentrations do not decline with marginal intakes, between 4 and 6 mg/d, and a decline in serum zinc concentrations may reflect inflammation or infection rather than low zinc intakes (9). Length-for-age is considered the best functional growth outcome for estimating zinc deficiency because it is the primary response to increased zinc intake (10).

Currently, there is no evidence-based method to determine the amount, frequency, and duration of zinc supplementation required to improve the growth of stunted infants who are considered to be zinc deficient. We hypothesized that mathematical models of zinc metabolism would be an effective strategy to predict the growth response when those infants are given zinc supplements.
for identifying protocols to improve growth in zinc-deficient infants. Mathematical models are used routinely to develop dosing regimens for drugs, but they have also been used to determine intakes to relieve a nutrient deficiency, namely vitamin A (11). Metabolism is a highly regulated, complex system, and perturbing one aspect causes a cascade of homeostatic responses. Those numerous responses make it difficult to predict the effect of changing zinc intakes on the homeostatic responses, but modeling and simulation procedures can be used to predict the outcomes (12). Mathematical models of zinc metabolism have been developed for neonates (13, 14), children (15), and adults (16–18). In addition, some aspects of zinc metabolism (i.e., absorption and endogenous excretion) have been measured in infants fed different amounts of zinc (19). However, a dynamic model of zinc metabolism that would provide a basis for protocols to replenish zinc pools in zinc-deficient infants does not exist. The aim of this study was to develop a dynamic model for zinc metabolism in infants and to use that model to predict the growth response when stunted, zinc-deficient infants are given zinc supplements.

METHODS

Modeling was performed by using the WinSAAM software (NIH) (20, 21). Initially, a kinetic, or steady state, model was created for healthy 9-mo-old infants (described below). This model was expanded into a dynamic model by adding functions that describe the changes in zinc absorption and excretion with changes in zinc intake, and that represent growth. Parameter values of the model were then set to represent stunted, zinc-deficient infants by using the WHO definition of stunting as length-for-age z score (LAZ) < −2 SDs of the WHO Child Growth Standards median (22) and of zinc deficiency as plasma zinc < 65 µg/dL (23). Then, various amounts of zinc supplementation were simulated by using the “QO feature” of WinSAAM (21). This feature sets the value of a compartment to specified values at specified times and is useful for simulating drug dosing regimens (24). In this study, the QO feature enabled variations of the amount, timing, and duration of zinc supplementation to be tested for improving growth or plasma zinc concentrations.

The dynamic model predictions of plasma zinc, weight, length, weight-for-age z score (WAZ), LAZ, and weight-for-length z score (WLZ), calculated by using equations posted on the WHO website (www.who.int/childgrowth/en), were compared with literature results of infants receiving supplemental zinc (i.e., the model prediction was compared with the mean result of each study). We note that the model was not fitted to the observed data, because the published data were from heterogeneous populations.

RESULTS

Development of a steady state model of zinc metabolism for infants aged 9 mo

Published kinetic models of zinc metabolism in adults (25) and neonates (13, 14) (Figure 1), together with literature data on tissue zinc concentration and tissue weights for infants (Table 1), were used to create a kinetic model (with time-invariant parameters) for zinc metabolism in 9-mo-old healthy infants (Figure 1). Inputs for the kinetic model were infant sex, age, weight, length, and plasma zinc concentration (Table 2).

We initially tested the model with the adult transfer coefficient values (25). A transfer coefficient, $L(i,j)$, is the fraction moving into compartment $i$ from compartment $j$ per day. (The value of a transfer coefficient can be $> 1$ if the source pool turns over $> 1$ time/d.) The adult kinetic parameter values fit the infant zinc tissue masses, except that to fit the red blood cell (RBC) zinc mass, it was necessary to reduce the zinc uptake into RBCs from plasma [$L(5,1)$; Figure 1] to 1/d in infants compared with...
2.4/d in adults. In addition, the infant model had only one RBC zinc pool, whereas there are 2 RBC pools in adults (25). To fit the muscle zinc mass in infants, uptake by muscle from plasma [L(3,1); Figure 1] was set at 2.375/d, which is higher than in adults (1.51/d) but lower than in neonates (26/d) (13, 14). The incorporation of zinc into all tissues by growth, represented in the baseline kinetic model, was divided between tissue pools in the dynamic model, described below.}

The values used by the IOM (33) for complementary foods. Two other pathways (RBC exchange and release from muscle) have been identified as sites of zinc regulation in adults (25). However, they were not included in the infant model due to lack.

Conversion to a dynamic model by the addition of functions for zinc absorption, endogenous excretion, and growth

To enable changes in zinc pools to be modeled over time in response to changes in zinc intake, a tracée model was set up with the use of the same parameter values as the kinetic model described above, but with initial conditions equated to the pool masses calculated by the baseline kinetic model.

Absorption was modeled by using a saturable function for absorbed compared with ingested zinc (19):

\[ \text{Absorbed Zn (mg/d)} = \left( A_{\text{max}} \times \frac{\text{ZI}}{} \right) \left( \frac{\text{IA}_{50} + \text{ZI}}{} \right) \]

where \( A_{\text{max}} \) is maximal absorption of zinc (1.9 mg/d for infants), ZI is zinc intake (milligrams per day), and \( \text{IA}_{50} \) is the quantity of zinc (milligrams per day) required for half-maximal absorption.

**TABLE 1**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Wet weight, g</th>
<th>Body weight, %</th>
<th>Wet weight(^{1}), 1 (\mu)g/organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>636</td>
<td>7.1</td>
<td>43</td>
</tr>
<tr>
<td>Brain</td>
<td>178</td>
<td>2.0</td>
<td>13.94</td>
</tr>
<tr>
<td>Heart</td>
<td>39</td>
<td>0.4</td>
<td>30.8</td>
</tr>
<tr>
<td>Kidney</td>
<td>39</td>
<td>0.4</td>
<td>19</td>
</tr>
<tr>
<td>Liver</td>
<td>229</td>
<td>2.6</td>
<td>34</td>
</tr>
<tr>
<td>Lung</td>
<td>127</td>
<td>1.4</td>
<td>12</td>
</tr>
<tr>
<td>Muscle</td>
<td>2225</td>
<td>25.0</td>
<td>108</td>
</tr>
<tr>
<td>Plasma</td>
<td>369</td>
<td>4.1</td>
<td>1.1</td>
</tr>
<tr>
<td>RBC(^{6})</td>
<td>280</td>
<td>3.1</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>4778</td>
<td>53.7</td>
<td>—</td>
</tr>
<tr>
<td>Whole body</td>
<td>8900</td>
<td>100</td>
<td>31.7</td>
</tr>
</tbody>
</table>

\(^{1}\)WHO median body weight (27).

\(^{2}\)Tissue weights are percentages of body weight for adults (28).

\(^{3}\)Tissue zinc (microgram per gram of dry weight) for bone, kidney, liver, and lung were from Erickson et al. (29) and tissue percentage wet weight was from Casey and Robinson (30).

\(^{4}\)For brain and heart, value is the assumed adult concentration based on White et al. (31).

\(^{5}\)Muscle mass and zinc concentrations were from Cheek et al. (32) for a 72-cm infant; White et al. (31) reported muscle at 25% of body weight at birth, and they assumed adult composition after 6 mo.

\(^{6}\)RBC, red blood cell.

**TABLE 2**

<table>
<thead>
<tr>
<th>Weight, kg</th>
<th>Length, cm</th>
<th>Plasma zinc, (\mu)g/dL</th>
<th>Zinc absorption, fraction</th>
<th>Zinc, mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.9</td>
<td>72</td>
<td>80–100(^{4})</td>
<td>0.3(^{5})</td>
<td>0.3</td>
</tr>
<tr>
<td>8.9 (7.9)</td>
<td>72 (67.5)</td>
<td>90 (60)</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

\(^{1}\)EAR, Estimated Average Requirement; IOM, Institute of Medicine; LAZ, length-for-age z score; WLZ, weight-for-length z score.

\(^{2}\)Values used are IOM values for normal boys (33).

\(^{3}\)Values assumed for the model in Figure 1 for infants who are normal or, in parentheses, zinc-deficient and stunted (i.e., –2 SDs of LAZ, but normal WLZ and plasma zinc <65 \(\mu\)g/dL).

\(^{4}\)See Hess et al. (23).

\(^{5}\)The value used by the IOM (33) for complementary foods.

\(^{6}\)EAR used by the IOM for infants aged 7 mo to 3 y (33).

\(^{7}\)Calculated by the model shown in Figure 1.

\(^{8}\)Weight gain over 12 mo was 2.6 kg for normal WLZ infants but 2.45 kg for stunted infants, based on WHO values (34).

\(^{9}\)Change in length was calculated by assuming a 5-cm/kg increase in weight for normal infants (34); on the basis of the WHO growth charts for stunted children, a lower value (4 cm/kg) was used for calculating change in length in stunted infants. Specifically, for infants <-2 SDs of LAZ but with appropriate weight [i.e., SD0 WLZ (i.e., stunted but not wasted) (34)], we used the change in length over change in weight between 6 and 9 mo (i.e., in the period before age of 9 mo).

\(^{10}\)Weight increased at a rate of 1 g weight/30-\(\mu\)g increase in absorbed zinc, which was calculated from the average zinc concentration per gram of body weight (Table 1) and used for infants by Krebs and Hambidge (35). [We note that the IOM (33) used 20 \(\mu\)g Zn/g as the average concentration in infant tissues.]

\(^{11}\)With zinc supplementation, it was assumed that 30% of the increase in absorbed zinc was used for infant growth (calculated from reference 34).

(2.8 mg/d in infants aged <6 mo and 8 mg/d in adults) (19). With the use of Equation 1, we determined with 30% absorption at 2.2 mg of intake (described above) an IA\(_{50}\) of 3.5 mg/d for 9-mo-old infants.

Endogenous excretion was modeled by fitting a linear equation to endogenous fecal zinc data and absorbed zinc for term infants (19):

\[ \text{Endogenous excretion (mg/d)} = 0.98156 + 0.30479 \times \text{absorbed Zn (mg/d)} \] (2)

Urinary zinc excretion was set to increase as a function of zinc absorbed with the use of data in Alexander et al. (37);

\[ \text{Urine Zn excreted (mg/d)} = 0.1463 \times \text{Zn absorbed (mg/d)} \] (3)

Two other pathways (RBC exchange and release from muscle) have been identified as sites of zinc regulation in adults (25). However, they were not included in the infant model due to lack.
of data. In addition, it is unlikely that RBC exchange would affect whole-body zinc metabolism and growth in infants.

Functions were added to the model to account for the increases in the size of zinc pools occurring with growth. Growth was represented by increasing the fractional zinc uptake by tissues from plasma, in proportion to the zinc mass of each tissue pool. A function was included that limited growth during supplementation, such that once a stunted infant attained the length of a normal infant, growth then continued at the rate of a healthy infant. WAZ, WLZ, and LAZ were calculated with the use of published methods (27, 34).

### Evaluation of model: simulation of published studies

To test the model, 5 published studies of zinc supplementation in infants aged ~9 mo old (38–42) were simulated (Table 3). Baseline weight, length, and plasma zinc concentration (if measured) were entered as starting values. The amount of zinc administered, the frequency of dosing, and duration of supplementation varied between studies. The actual dosing regimen (e.g., if it was given 5 d/wk) was simulated. The model calculated changes in plasma zinc concentration, weight and length, WAZ, LAZ, and WLZ, and growth rates over time. WLZ was calculated at baseline and at the end of supplementation. The model predictions were compared with the observed values and are reported as differences from baseline. The comparison for plasma zinc is given for 2 studies in Figure 2. In a study by Wessells et al. (38), infants aged 6–23 mo in Burkina Faso were supplemented for 3 wk with 5 mg Zn/d. Initial plasma zinc concentrations indicated that the infants were zinc deficient (Table 3). Plasma zinc increases with zinc supplementation were within 22% of observed values (Figure 2). In a study by Weuhler et al. (39), for Ecuadorian infants who were older (<30 mo of age) and supplemented for 6 mo with 1 of 4 amounts of zinc daily (Table 3), the model-predicted net increases in plasma zinc compared with placebo with each dose were within 16% of the observed values (Figure 2).

Umeta et al. (40) supplemented Ethiopian infants aged 9 mo of age who were either stunted (LAZ < −2) or not stunted with 0 or 10 mg Zn/d for 6 d/wk for 6 mo. Plasma zinc concentrations, measured only at the end of the study, were normal for both groups (Table 3). The observed smaller increases in weight and length in the stunted compared with the nonstunted infants at the end of dosing were also predicted by the model (Table 4). The model-predicted increases in weight and length for the normal and stunted infants in the placebo group were within 30% of measured values (Table 4), but weight and length changes were overpredicted in the zinc-supplemented groups (e.g., the model predicted an increase in length of 11 cm in the stunted infants compared with the observed increase of 7 cm). One explanation could be that absorption was lower in the stunted infants. To test this, we reduced absorption by 50% and found that the predicted increases in weight and length in the stunted, supplemented group then matched the observed values (Table 4).

A study observed Vietnamese infants ranging in age from 6 to 24 mo who were not stunted and were supplemented for 3 mo with either 17 mg Zn 1 time/wk or 5 mg Zn/d for 5 d/wk (41). The model predicted the observed increases in plasma zinc concentration after supplementation (Table 4). In addition, the small changes in weight and length predicted by the model were similar to the reported values measured 3 mo after the end of supplementation (Table 4). In another study in stunted infants given 10 mg Zn/d for 5 mo (42), the supplement significantly increased weight and length, as was predicted by the model (Table 4).

### Model predictions: simulations of various zinc supplementation regimens

The model was used to simulate changes in weight, length, and plasma zinc concentrations in stunted, zinc-deficient infants,
A model for predicting changes in plasma zinc concentrations, weight, and length was developed for stunted, zinc-deficient 9-mo-old infants who receive various amounts of supplemental zinc. The model predictions of changes in plasma zinc, linear growth, and weight gain were compared with 5 published studies of the changes observed when supplemental zinc was provided (38–42); 2 of the studies only reported changes in plasma concentration. The model predictions matched changes in plasma zinc with the reported values as well as changes in weight and length with the published growth responses (41, 42). In one of those studies (41), infants were supplemented with minerals and multivitamins to ensure adequate micronutrient intakes. In a study in which other vitamin and minerals were not given (40), the effects of zinc on growth were more modest than when multiple micronutrient supplements were provided (42), suggesting that other nutrient deficiencies may have limited the growth response to zinc. For that study (40), the model predicted a gain of 2.88 kg; the observed gain was 1.73 kg over the 6-mo supplementation with 10 mg Zn/d. On the basis of the assumption that 30% of the absorbed zinc was used for a gain in tissue containing 30 µg Zn/kg, this would suggest that only 8% (152 mg of the 1800-mg intake) was absorbed. If zinc absorption is reduced by ~50% in infants aged 18–24 mo who are at risk of environmental enteric dysfunction (43). The model is designed to increase growth when zinc intake is increased. Therefore, it is
### TABLE 4
Comparison of published and model-simulated values

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Plasma zinc, µg/dL</th>
<th>Weight, kg</th>
<th>Length, cm</th>
<th>WAZ</th>
<th>LAZ</th>
<th>WLZ</th>
<th>g/d</th>
<th>cm/mo</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 mg Zn/d</td>
<td>—</td>
<td>1.02</td>
<td>6.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Model-calculated</td>
<td>—</td>
<td>1.03</td>
<td>5.1</td>
<td>0.0</td>
<td>—</td>
<td>0.3</td>
<td>0.1</td>
<td>5.7</td>
<td>0.9</td>
</tr>
<tr>
<td>10 mg Zn/d</td>
<td>—</td>
<td>1.19</td>
<td>6.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.0</td>
<td>11.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Model-calculated</td>
<td>—</td>
<td>1.81</td>
<td>9.1</td>
<td>0.8</td>
<td>1.3</td>
<td>0.2</td>
<td>0.2</td>
<td>10.1</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Stunted</strong></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0 mg Zn/d</td>
<td>—</td>
<td>0.95</td>
<td>2.9</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Model-calculated</td>
<td>—</td>
<td>0.95</td>
<td>3.8</td>
<td>0.1</td>
<td>—</td>
<td>0.6</td>
<td>0.0</td>
<td>5.3</td>
<td>0.6</td>
</tr>
<tr>
<td>10 mg Zn/d</td>
<td>—</td>
<td>1.73</td>
<td>7.0</td>
<td>0.4</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
<td>9.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Model-calculated</td>
<td>—</td>
<td>2.88</td>
<td>11.5</td>
<td>2.1</td>
<td>2.5</td>
<td>0.0</td>
<td>0.0</td>
<td>16.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Alternate²</td>
<td>—</td>
<td>1.92</td>
<td>7.7</td>
<td>1.2</td>
<td>0.9</td>
<td>0.1</td>
<td>0.1</td>
<td>10.6</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Difference from baseline</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stunted</td>
<td>—</td>
<td>0.17</td>
<td>2.5</td>
<td>0.2</td>
<td>0.0</td>
<td>0.1</td>
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<td>5.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Model-calculated</td>
<td>—</td>
<td>1.03</td>
<td>5.1</td>
<td>0.0</td>
<td>—</td>
<td>0.3</td>
<td>0.1</td>
<td>5.7</td>
<td>0.9</td>
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<tr>
<td>Difference from nonstunted</td>
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<td></td>
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</tr>
<tr>
<td>Normal</td>
<td>—</td>
<td>—1.07</td>
<td>—7.6</td>
<td>—1.1</td>
<td>—2.8</td>
<td>0.5</td>
<td>—0.4</td>
<td>—0.4</td>
<td></td>
</tr>
<tr>
<td>Model-calculated</td>
<td>—</td>
<td>—1.07</td>
<td>—6.8</td>
<td>—1.2</td>
<td>—2.8</td>
<td>0.2</td>
<td>—0.4</td>
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</tr>
<tr>
<td>Stunted</td>
<td>—</td>
<td>—3.65</td>
<td>—4.6</td>
<td>—0.4</td>
<td>—1.7</td>
<td>0.8</td>
<td>—2.1</td>
<td>0.1</td>
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<tr>
<td>Model-calculated</td>
<td>—</td>
<td>0.17</td>
<td>—2.5</td>
<td>0.2</td>
<td>0.0</td>
<td>0.1</td>
<td>0.1</td>
<td>5.9</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Difference from baseline</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 mg Zn 1 d/wk</td>
<td>—</td>
<td>27.0</td>
<td>0.10</td>
<td>1.00</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Model-calculated</td>
<td>—</td>
<td>16.5</td>
<td>0.00</td>
<td>0.40</td>
<td>0.0</td>
<td>0.2</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5 mg Zn/d</td>
<td>—</td>
<td>21.0</td>
<td>0.10</td>
<td>0.10</td>
<td>0.0</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Model-calculated</td>
<td>—</td>
<td>18.1</td>
<td>0.13</td>
<td>0.23</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.7</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Difference from unsupplemented</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg Zn/d</td>
<td>—</td>
<td>—0.6</td>
<td>3.6</td>
<td>—0.2</td>
<td>—0.1</td>
<td>—0.2</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Model-calculated</td>
<td>—</td>
<td>—1.1</td>
<td>4.2</td>
<td>0.0</td>
<td>0.2</td>
<td>0.0</td>
<td>0.2</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>Difference from baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stunted</td>
<td>—</td>
<td>—0.36</td>
<td>—4.6</td>
<td>—0.4</td>
<td>—1.7</td>
<td>0.8</td>
<td>—2.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Model-calculated</td>
<td>—</td>
<td>0.17</td>
<td>—2.5</td>
<td>0.2</td>
<td>0.0</td>
<td>0.1</td>
<td>0.1</td>
<td>5.9</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Difference from unsupplemented</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg Zn/d</td>
<td>—</td>
<td>—0.40</td>
<td>1.1</td>
<td>0.3</td>
<td>0.3</td>
<td>0.1</td>
<td>3.3</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Model-calculated</td>
<td>—</td>
<td>0.45</td>
<td>1.8</td>
<td>0.4</td>
<td>0.7</td>
<td>0.3</td>
<td>3.7</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

1LAZ, length-for-age z score; Ref, reference; WAZ, weight-for-age z score; WLZ, weight-for-length z score.
2Simulation with absorption function multiplied by 0.5.

not able to reproduce the results of studies in which zinc had no effect on growth (44, 45). However, it can be used to test theories as to why no growth response occurred, such as low absorption.

The model predicts the metabolic responses to zinc supplementation on the basis of the amount, frequency, and duration of zinc dosing. Initial predictions suggest that frequent doses are more effective at promoting growth than are large doses given less frequently. A higher daily dose (e.g., 10 mg/d) normalized length and weight 3 mo earlier than did 5 mg/d. In addition, smaller amounts (5 mg) given daily were more effective than a larger amount (10 mg) given weekly. Thus, the model supports quantitatively the recommendation to give smaller, more frequent doses (46). Possibly, larger doses given less frequently trigger homeostatic responses, such as increased excretion rather than increasing the amount of zinc absorbed for deposition in body tissues and increasing growth. The model also showed the importance of the length of time that the zinc dose is provided; if the period is too short (e.g., 3 mo compared with 6 mo), the plasma zinc concentrations do not reach normal values.

The model is based on the assumption that the metabolic regulation of zinc in stunted, zinc-deficient infants is similar to that of normal infants. When normal infants aged 1–8 mo were fed 2 amounts of zinc in a crossover design, zinc balance was achieved with a lower zinc intake by increasing fractional absorption and decreasing endogenous excretion (47). Kinetic studies in young piglets also showed that a reduction in zinc intake to 15% of the recommended amount caused an increase in fractional absorption to maintain weight gain similar to that of an adequate-zinc group (48). Studies in healthy, breastfed 5-mo-old infants fed complementary foods with varying zinc intakes showed that fractional zinc absorption increased with lower zinc intakes, but the amount absorbed from the low-zinc diet was insufficient to meet physiologic requirements, suggesting that absorption may not compensate for low zinc intakes in healthy infants (46). However, other...
homeostatic responses (i.e., endogenous fecal excretion) were not measured.

One limitation of our model is that the calculated increase in length is a constant function of weight gain. However, length and mass may change differently over time (e.g., LAZ declines more sharply from birth to age 24 mo than does WAZ) (49). Some studies report that there is a lag between linear growth and weight gain in infants, and that during catch-up growth weight gain takes precedence over length gain (50). Thus, it appears that after repletion of infants who experience growth-faltering, muscle recovery occurs before bone growth. Our adult tracer studies are consistent with that conclusion (i.e., that muscle zinc release is regulated and conserved when zinc intake is low) (25). This is not seen in bone. Both animal and human studies show that muscle zinc is retained with zinc deficiency, whereas bone loses zinc (12). On the basis of these observations, when zinc-deficient infants who are stunted but not wasted are given zinc we predict that bone growth would be stimulated more than muscle gain. Due to the lack of data, we were unable to model differential rates of bone and muscle growth with zinc repletion. However, the potential effect of incorporating these rates into the model would likely have a small effect of the predicted gain in weight and length. Strengths of the model are that it is physiologically based on human data, it is parameterized for infants, and it includes nonlinear functions for zinc metabolic pathways known to be regulated by zinc intake (absorption and excretion) and for growth of tissues.

The comparison of simulated results with reported values was challenging because the pediatric populations studied varied widely in terms of age, health, and nutritional status (38–42). For example, the ages often varied from 6 to 36 mo. Because our model simulates values for 9-mo-old infants, it was difficult to compare simulated to published values because the growth rates are faster at 9 mo than at 20 mo (27). In addition, the growth rates frequently are not analyzed according to sex, even though boys have different growth rates than girls (27). Finally, the proportion of zinc-deficient infants in a study can vary widely [e.g., 27–40% (39) to >70% (38)]. However, the model can be readily modified to simulate different degrees of stunting and zinc deficiency in both boys and girls by adjusting the initial weight and baseline growth rates (49). It is important to keep in mind that supplements may have a limited effect on growth in infants >24 mo of age (49).

In summary, we developed a dynamic model of zinc metabolism for infants. The model predicts growth on the basis of the amount, frequency, and length of zinc supplementation for 9-mo-old stunted infants who are zinc-deficient based on their diet and plasma zinc concentrations. The predicted response can be applied to infants who receive supplemental zinc administered alone or as a part of multiple micronutrient powder. Because weight and length changes are approximately linear between 9 and 24 mo of age (27), the model can be used for infants in that age range. In the future, our model predictions of zinc supplementation need to be evaluated in homogenous groups of stunted infants with respect to age, sex, and zinc status. That information will improve predicted amounts of supplemental zinc, and it will identify the population subgroups (e.g., infants with plasma zinc and LAZ below defined thresholds) most likely to respond to zinc supplementation. Eventually, this dynamic model can be used to
develop evidence-based clinical protocols for zinc supplementa-
tion trials to treat zinc deficiency in various pediatric populations
around the world.

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ponsibility for final content; and all authors: wrote the manuscript, and read
and approved the final manuscript. None of the authors declared a conflict of
interest.

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Investigating biological systems using modeling: strategies and


