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A Mathematical Model of Zinc Absorption in Humans As a Function of Dietary Zinc and Phytate,[1,2]

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Abstract

The quantities of zinc and phytate in the diet are the primary factors determining zinc absorption. A mathematical model of zinc absorption as a function of dietary zinc and phytate can be used to predict dietary zinc requirements and, potentially, enhance our understanding of zinc absorption. Our goal was to develop a model of practical and informative value based on fundamental knowledge of the zinc absorption process and then fit the model to selected published data to assess its validity and estimate parameter values. A model of moderate mathematical complexity relating total zinc absorption to total dietary zinc and total dietary phytate was derived and fit to 21 mean data from whole day absorption studies using nonlinear regression analysis. Model validity, goodness of fit, satisfaction of regression assumptions, and quality of the parameter estimates were evaluated using standard statistical criteria. The fit had an R^2 of 0.82. The residuals were found to exhibit a normal distribution, constant variance, and independence. The parameters of the model, A_{MAX}, K_R, and K_P, were estimated to have values of 0.13, 0.10, and 1.2 mmol/d, respectively. Several of these estimates had wide CI attributable in part to the small number and the scatter of the data. The model was judged to be valid and of immediate value for studying and predicting absorption. A version of the model incorporating a passive absorption mechanism was not supported by the available data.

Introduction

It is widely accepted that, of the numerous dietary factors known or suspected to affect zinc absorption, zinc and phytate (inositol hexaphosphate) content have the greatest effect (1). An understanding of these factors and the underlying mechanisms and quantification of their effects is essential for advancing our knowledge of the zinc absorption process and for predicting zinc absorption for a variety of populations and diets, a necessary step in determining zinc dietary requirements and assessing the risk of zinc deficiency. Mathematical modeling of zinc absorption as a function of dietary zinc and phytate can play a valuable role in achieving these goals. A number of investigators have used mathematical functions and regression analysis to model the observed relations between zinc absorption and various dietary components, including zinc, phytate, and the phytate:zinc molar ratio (1–14). The nature of these data and models and the experimental and analytical methods used varied greatly and most did not attempt to characterize the combined effects of dietary zinc and phytate on zinc absorption. Two documents, from the WHO (5) and the International Zinc Nutrition Consultative Group (IZiNCG)3 (1), have described advances in modeling both zinc and phytate data from human studies for the purpose of estimating dietary requirements. Wing et al. (6) presented a model of mineral availability related to mineral and phytate dietary content that they applied to zinc, iron, and cadmium data from rats.

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[2]Supplemental Figures 1 and 2 are available with the online posting of this paper at jn.nutrition.org.

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We report here the development of a new mathematical model of the quantity of zinc absorbed per day as a function of dietary zinc and phytate. There are several characteristics of this model and its development that, taken together, make it novel. First, the model was derived from a biochemical conception of the absorption process. A mathematical model having a foundation in the physical process being modeled is potentially more informative and more likely to be valid than a model utilizing a mathematical function that merely mimics the behavior of the data. Furthermore, given its foundation in the physical process, the model is amenable to revision based on additional knowledge of that process. Second, absorbed zinc was modeled as a function of both dietary zinc and phytate. Third, the variables modeled were the total daily dietary zinc (*TDZ*) and phytate (*TDP*) ingested and total daily absorbed zinc (*TAZ*) from all the meals over an entire day. The measurement of absorption over a full day is understood to be more meaningful than single meal measurements. And the modeling of quantities ingested and absorbed is likely to be advantageous to modeling ratios of those quantities, i.e. fractional absorption or phytate:zinc molar ratio. Fourth, nonlinear regression analysis was used to fit the model to data. Because zinc absorption is primarily a saturable, carrier-mediated process (15–17), the relation of absorbed to dietary zinc is nonlinear. The effect of phytate on absorption is also expected to be nonlinear. Analyzing such relations with nonlinear regression is generally preferred to using data transformation and linear regression, unless the transformation is necessitated for other reasons. Fifth, because validation is an important component of model development, the model was submitted to an assessment of its validity based primarily on its fit to selected data from the literature.

The development of this model is a continuation of our application of saturation response modeling, derived from pharmacodynamic data analysis, to zinc absorption data (9,11,13,14).

Materials and Methods

Derivation of model

Figure 1 illustrates the biochemical basis for the model. The diagram shows the binding interactions central to the transporter-mediated absorption process (15–17) taking place in the small intestine. Zinc-receptor binding is shown to be a reversible reaction, assumed to be in equilibrium. This assumption appears reasonable considering the rate of zinc uptake by intestinal transporters (16) and the interval over which absorption from the intestine occurs (18). This receptor binding reaction should be understood to represent the interaction of intestinal zinc with a complex absorption process that actually involves multiple transporter proteins and steps. Phytate is shown to function as a chemical antagonist, competing for the free zinc to form the insoluble zinc-phytate complex in a reversible binding reaction, also in equilibrium. The K_1 and K_2 symbols denote the association and dissociation rate constants of the binding reactions. Additional kinetic details of this process, e.g. a rate constant for the movement of zinc-transporter complexes from the reaction equilibrium into the enterocyte, are ignored for the time being due to complexity and lack of data to support their inclusion. Although this conception of zinc absorption is, necessarily, rudimentary and simplistic, it can provide a well-founded basis for a preliminary model.

The derivation of a mathematical model from the diagram of Figure 1 applies the law of mass action and occupancy theory from pharmacokinetic/pharmacodynamic modeling (19,20) and begins with the equations describing the 2 binding reactions:

$$K_{P1} \cdot [P_u] \cdot [Zn_u] = K_{P2} \cdot [ZnP] \quad \text{(Eq. 1)}$$

$$K_{R1} \cdot [R_u] \cdot [Zn_u] = K_{R2} \cdot [ZnR], \quad \text{(Eq. 2)}$$

where the *P* represents phytate, *Zn* represents zinc, *R* represents transport receptors, and *ZnP* and *ZnR* are the zinc-phytate and zinc-receptor complexes, respectively. The u subscript indicates the free (unbound) form of the species. It is assumed that the transport receptors have a single zinc binding site and that each phytate molecule binds only 1 zinc ion. Although phytate is capable of binding multiple divalent cations, the chemical environment of the intestine, notably the pH and presence of other cations and ligands, precludes the possibility of all the binding sites being occupied by zinc ions. In fact, it is speculated that, practically, phytate binds a single zinc ion in vivo (Boyd O'Dell, University of Missouri, personal communication). It is conceivable that, as the model evolves and is applied to additional data, it may be modified to accommodate binding of multiple zinc ions; however, as the binding constant is different for each additional ion bound, model complexity will become an issue. There are no assumptions regarding the relative concentrations of any of the species involved in the binding reactions. After the substitution of the following equalities and approximation

$$[P_u] = [P_t] - [ZnP] \approx [P_t] \quad \text{(Eq. 3)}$$

$$[R_u] = [R_t] - [ZnR] \quad \text{(Eq. 4)}$$

$$[Zn_u] = [Zn_t] - [ZnR] - [ZnP] \quad \text{(Eq. 5)}$$

$$K_P = K_{P2} / K_{P1} \quad \text{(Eq. 6)}$$

$$K_R = K_{R2} / K_{R1}. \quad \text{(Eq. 7)}$$

Equations 1 and 2 are rearranged to

$$[P_t] \cdot ([Zn_t] - [ZnR] - [ZnP]) = K_P \cdot [ZnP] \quad \text{(Eq. 8)}$$

$$([R_t] - [ZnR]) \cdot ([Zn_t] - [ZnR] - [ZnP]) = K_R \cdot [ZnR]. \quad \text{(Eq. 9)}$$

The subscript t indicates the total quantity of the species. K_P and K_R are the equilibrium dissociation constants of zinc-phytate and zinc-receptor binding, respectively.

Equation 3 introduces an approximation, that $P_u \approx P_t$, which is necessary to simplify the model so that it is of practical use. Without this approximation, it is anticipated that an exact solution of the model would be so complex as to be of limited practical value. The approximation is good to the extent that $P_t \gg ZnP$. Once the model has been fit to the data and the parameters estimated, the closeness of the approximation can be assessed using this relation derived from the equations above:

$$\frac{P_t}{ZnP} = \frac{K_P \cdot (R_t - ZnR)}{K_R \cdot ZnR} + 1. \quad \text{(Eq. 10)}$$

Furthermore, with this information, an evaluation of the sensitivity of the model to the approximation can be made.

Equation 8 is solved for *ZnP* and substituted into Equation 9, which is then solved for *ZnR*.

Finally, because all species occupy the same luminal volume, units of concentration are changed to molar rates and the equivalent experimental variables and a model parameter are substituted for the biochemical terms as follows:

$[P_t] = TDP$

$[Zn_t] = TDZ$

$[ZnR] = TAZ$

$[R_t] =$ maximum absorbed zinc(A_{MAX}).

All are in units of millimoles per day. The resulting equation for the model is:

$$TAZ = 0.5 \cdot \left(A_{MAX} + TDZ + K_R \cdot \left(1 + \frac{TDP}{K_P}\right) - \sqrt{\left(A_{MAX} + TDZ + K_R \cdot \left(1 + \frac{TDP}{K_P}\right)\right)^2 - 4 \cdot A_{MAX} \cdot TDZ}\right). \quad \text{(Eq. 11)}$$

This is a trivariate model having 2 independent (predictor) variables, *TDZ* and *TDP*, with *TAZ* being the dependent (response) variable. The model has 3 parameters: A_{MAX}, K_R, and K_P.

The model equation may be modified to use fractional absorption of zinc (*FAZ*) instead of *TAZ*, or to use phytate:zinc molar ratios (R_{PZ}) instead of *TDP* to make predictions after the parameters have been estimated:

$$FAZ = \frac{0.5}{TDZ} \cdot \left(A_{MAX} + TDZ + K_R \cdot \left(1 + \frac{TDP}{K_P}\right) - \sqrt{\left(A_{MAX} + TDZ + K_R \cdot \left(1 + \frac{TDP}{K_P}\right)\right)^2 - 4 \cdot A_{MAX} \cdot TDZ}\right). \quad \text{(Eq. 12)}$$

$$TAZ = 0.5 \cdot \left(A_{MAX} + TDZ + K_R \cdot \left(1 + \frac{R_{PZ} \cdot TDZ}{K_P}\right) - \sqrt{\left(A_{MAX} + TDZ + K_R \cdot \left(1 + \frac{R_{PZ} \cdot TDZ}{K_P}\right)\right)^2 - 4 \cdot A_{MAX} \cdot TDZ}\right). \quad \text{(Eq. 13)}$$

A version using both *FAZ* and R_{PZ} may be also created.

It is also possible without much difficulty to augment the model to include a passive absorption mechanism, observed in animals and thought to possibly play a minor role in zinc absorption in humans (15,16). On the assumption that passive absorption is a nonmediated diffusion process and proportional to both the quantity of unbound zinc in the intestinal lumen and a passive nonmediated absorption coefficient (*NMA*), the model becomes:

$$TAZ = \left(0.5 \cdot \left(A_{MAX} + TDZ + K_R \cdot \left(1 + \frac{TDP}{K_P}\right) - \sqrt{\left(A_{MAX} + TDZ + K_R \cdot \left(1 + \frac{TDP}{K_P}\right)\right)^2 - 4 \cdot A_{MAX} \cdot TDZ}\right)\right) \cdot \left(1 - \frac{NMA \cdot K_P}{K_P + TDP}\right) + \frac{NMA \cdot K_P \cdot TDZ}{K_P + TDP}. \quad \text{(Eq. 14)}$$

With *NMA*, this model has 4 parameters. It can be expected that the small number of available data are inadequate to currently support the additional parameter.

Selection of data

The 15 data points compiled by the IZiNCG from 9 published studies (21–29) provided the majority of data for our analyses. Their data selection criteria were: *1*) radio- or stable-isotope studies that estimated true zinc absorption from total (daily) diets by correcting for intestinal losses of endogenous zinc; *2*) studies of typical mixed, refined vegetarian, or unrefined, cereal-based diets, but not those that used semipurified formula diets or diets with exogenous zinc salts added; and *3*) studies with male or female adults, with no geographic limitations (1). In addition to these data, we included 6 data points from 2 other studies (8,30), including 1 that used a liquid formula diet. These latter data did not meet the 2nd criterion of the IZiNCG; otherwise, the additional data were in agreement with the criteria. Fortunately, these additional data extended the range of *TDP* beyond that of the IZiNCG data.

Each of the 21 data were a mean of the results from 4 to 21 adult subjects. Mean data were used, because the individual data from many of the studies were not available. All subjects were apparently healthy and assumed to be in normal zinc status. No data from studies of children were included. A total of 105 subjects participated in the 11 studies. *TAZ* was always measured using established isotope techniques, as specified in the first selection criterion. *TDZ* was determined by chemical analysis of representative diets in most studies, although at least 1 study relied on the calculation of dietary zinc from diet records. In the case of the liquid formula diet, a measured quantity of zinc was added during diet composition. In a majority of the studies, *TDP* was calculated from diet composition by the authors of the studies or by the IZiNCG, but phytate was analyzed in 2 of the studies and a known quantity was added to the liquid formula diet. In most studies, the subjects were on the test diets for at least 7 d prior to absorption measurements. Dietary calcium and protein data were also available for 14 of the data.

Data analysis

The model was fit to the data using nonlinear regression analysis with the programs DataFit (version 8.1, Oakdale Engineering) and SigmaPlot (version 10.0, Systat Software). There was no weighting of data for the regression analyses. DataFit provided regression statistics and 3-dimensional graphing of the data and model. SigmaPlot calculated additional regression statistics. Other statistical analyses and 2-dimensional graphing were performed with GraphPad Prism (version 4.03, GraphPad Software). The regression assumptions of normality, constant variance, and independence (lack of correlation) of the residuals were tested as follows. Distribution of the residuals was evaluated with the Kolmogorov-Smirnov and Shapiro-Wilk normality tests. Constant variance was tested by computing Spearman rank correlation between the absolute values of the residuals and the *TAZ* values. Independence was determined using the runs test and the Durbin-Watson test for serial correlation. Statistical significance was defined to be at the level of 0.05.

Results

The regression analysis (using Eq. 11) converged to what appears to be the true least-squares fit without difficulty. A variety of initial values were used and all successful analyses converged to the solution described here. The data and fitted model are illustrated graphically in Figure 2, where the data points are represented by round symbols and the model by a (gray) surface. The vertical ‘‘stems’’ on the data symbols indicate the distance, up or down, from each datum to the surface, i.e. the residual. The origin (0,0,0) of the graph is, unconventionally, positioned at the right-rear of the graph. This orientation provides a clearer, more informative perspective of the data and model. Also, the model has been extrapolated beyond the range of the data to demonstrate its behavior as *TDZ* approaches 0.

The resulting parameter estimates with the 95% CI shown in parentheses are:

$$A_{MAX} = 0.13(0.034 \text{ to } 0.23)$$
$$K_R = 0.10(-0.073 \text{ to } 0.28)$$
$$K_P = 1.2(-0.36 \text{ to } 2.8).$$

The P(t) values, the probability of being wrong in concluding that the parameter value is not 0, of the estimates are 0.011, 0.24, and 0.12 for A_{MAX}, K_R, and K_P, respectively. The R^2 is 0.82 and the adjusted version (R_a^2), taking into account the degrees of freedom, is 0.79. The sum of squares of the residuals is 0.0011. One datum deviated noticeably from the model and was flagged as a possible outlier based on the magnitude of its standardized, and Studentized, residual. Although it was not removed for fitting the model, evaluations of the model residuals were performed with and without the discrepant point.

Examination of the residual normal probability plot with (Fig. 3) and without the discrepant datum indicated a normal distribution, although inclusion of the questionable point (upper right) did skew the plot noticeably. The Kolmogorov-Smirnov and Shapiro-Wilk normality tests showed the residuals to have a normal distribution with P-values of 0.078 and 0.052 (>0.10 and 0.73 without the discrepant datum), respectively. The residuals passed a test for constant variance using Spearman rank correlation ($P = 0.68$). Runs tests were applied to the residuals relative to *TDZ*, *TDP*, and predicted *TAZ*, giving P-values of 0.25, 0.61, and 0.61, respectively, demonstrating independence, i.e. that the number of runs was similar to that expected for randomly distributed data in each case. A Durbin Watson test value of 1.78 also indicated a lack of serial correlation, although this test usually applied to data that were equally spaced relative to the predictor variables. In addition to the formal tests, examination of the graphs of the residuals relative to *TDZ*, *TDP*, and predicted *TAZ* (Fig. 4*A*–*C*) confirmed the findings of constant variance and independence. The only hint of nonconstant variance occurs in Figure 4*B* and is probably attributable to the clustering of the data in the low *TDP* range. And, the only discernable nonrandomness in the residual plots is that the residuals are negative at high x-axis values. This is attributable to the discrepant point discussed above and is no longer evident when the point is removed. In summary, all the analyses indicated that the residuals met the assumptions of normality, constant variance, and independence.

Having values for the parameters, it is possible to use the model to predict *TAZ* or *FAZ* for any zinc and phytate dietary content in healthy adults. For example, a family of curves predicting *TAZ* from *TDZ* and R_{PZ} derived with Equation 13 is illustrated in Figure 5. Additional examples of prediction curves, from Equations 11 and 12, are provided in Supplemental Figure 1.

Regression analyses were also performed with Equations 12 and 14. The analysis using Equation 12, where FAZ is the response variable, produced a result inferior to that from Equation 11. Whereas the parameter estimates and their CI were similar, the fit was not nearly as good, as indicated by an increased sum of squares of the residuals (0.066) and lower R^2 (0.61). As expected, the analysis using Equation 14 confirmed that the available data do not support inclusion of a passive absorption mechanism. Although the residual sum of squares (0.0010) and R^2 (0.82) were essentially unchanged, the parameter values were different and their CI much larger, e.g. A_{MAX} [95% CI] was estimated to be 0.33 (−1.91 to 2.57).

Regarding the approximation of Equation 3 and its evaluation with Equation 10, the ratio of P_t to *ZnP* was found to be 28 for the mean *TAZ* from the data and having a range of 8.1 to 108 for the range of *TAZ*, with the ratio being the lowest when *TAZ* is high. Under the worst case conditions, the effect on the accuracy of the model was estimated to be ~5%, i.e. at the high end of the *TAZ* range values produced by the model are 5% lower than without the approximation.

To investigate the possible role of calcium, sometimes quantified as the calcium*phytate/Zn molar ratio, or protein in zinc absorption in the presence of phytate (31), the dietary calcium, calcium*phytate/Zn molar ratio, and dietary protein data from 14 studies were plotted against the residuals (Supplemental Fig. 2). None of these data exhibited a relation with the residuals, suggesting these dietary factors did not affect zinc absorption in these studies. This is consistent with the IZiNCG findings (1).

Discussion

As we have acknowledged, and as is the case with all models of biological systems and processes, the model we have developed is a simplistic representation. Beyond our limited knowledge of the process, the few available data with which to validate the model would not have supported the incorporation of more detailed knowledge of the absorption mechanisms, as demonstrated by addition of a passive absorption pathway. Furthermore, much additional complexity would require the use of more sophisticated analytical or numerical methods to solve the model equations and risks limiting the practical value of the model for routine application. Even at the basic level of our model, we encountered the need to use an approximation to avoid impractical complexity. Though rudimentary, the model may be judged to be valid for its intended predictive and explanatory purposes using various criteria, including soundness of the basis and derivation of the model, goodness of fit to the data, reasonableness and quality of parameter estimates, comparison to other models, and applicability and usefulness in current research (32,33).

Figure 2 conveys essential information about the behavior of the model and its fit to the data. Although much of this information is presented here in other forms, the 3-dimensional representation best illustrates the distribution of the data in the predictor variable plane and the random nature of the residuals relative to all the variables. It is obvious from this graph that the model does not support the existence of a threshold for a phytate effect on absorption.

The goodness of fit as reflected in the R^2 of 0.82 is very supportive of the model, indicating that 82% of the variance in *TAZ* is explained by the model. Analyses of the residuals also confirmed the quality of the fit and adequacy of the model while testing the assumptions underlying the regression analysis. These assumptions, which must be met for the regression to be valid, are that the errors, as reflected in the residuals, exhibit a Gaussian (normal) distribution, constant variance, and independence. Evaluating independence is necessary to detect nonrandom behavior in the residuals, indicating a systematic deviation of the model from the data. The residuals passed all the tests and visual examinations, although the presence of a datum that deviated noticeably from the model caused some results to be marginal. This point and its large residual are evident in Figures 2–4. Although this datum looks suspiciously like an outlier, we have examined the study in which it was measured and found no reason to reject it as an outlier at this time. Therefore, the point was retained for fitting the model and estimating the parameters. However, because of its disproportionate effect on the analyses of the residuals, the analyses without the discrepant point are thought to more accurately reflect the error characteristics on the whole.

The uncertainties around the parameter estimates are large, although A_{MAX} may be considered to be adequately determined, because we can reasonably conclude that it is not 0 ($P = 0.011$). Though large uncertainty in the parameters is usually the result of a model having too many parameters (overparameterization) and collinearity of the parameters, it is not justified, or prudent, to simplify the model for the following reasons: *1*) The model is supported by the other measures of validity; *2*) the model is already of minimal complexity, given that there are 2 uncorrelated ($r = 0.09$) predictor variables and the relations are nonlinear and nonarbitrary; *3*) each of the parameters has a well-defined relation to an essential element of the absorption

process and cannot be eliminated without compromising the foundational validity of the model; and *4*) the current data are limited in number and exhibit variability that may related to the multiple laboratories, analytical methods, and experimental protocols involved. It is expected that the quality of the estimates will improve notably with additional data.

Regarding the values of the parameter estimates, we have found virtually no existing data with which to compare them, although it is noteworthy that the relative magnitude of the equilibrium dissociation constants, i.e. $K_P > K_R$, is consistent with that reported by Wing et al. (6) and with the deduction by O'Dell, from an experiment in which dietary EDTA alleviated the detrimental effect of phytate, that EDTA has a higher binding affinity for zinc than phytate and that mucosal receptors have a still higher affinity (Boyd O'Dell, University of Missouri, personal communication). Our previous application of a basic saturable response model (11) to the data used by the Food and Nutrition Board (7) estimated a value of 0.11 mmol/d for A_{MAX}, not significantly different ($P = 0.71$) from the 0.13 mmol/d estimated here. It should be noted that, although we expect that this model may be appropriate for application to data from any human population, the parameter values derived here characterize absorption in healthy adults with assumed normal zinc status and, therefore, caution should be exercised in interpreting their predictive application to other populations until additional data have been modeled. As well as the predictive uses of the model that the parameter estimates permit, it is possible that the parameter values themselves will provide information about absorption. Because A_{MAX} is related to the number of transport receptors and K_R and K_P quantify the association/dissociation characteristics of the binding reactions, application of the model may contribute to our limited knowledge of receptor regulation and binding chemistry as it relates to bioavailability.

The opportunities for comparing the model's predictions to other models are very limited. Not surprisingly, the *TAZ* predictions from our model agree with those of the IZiNCG model (1) with ±6% across the range of the data, but the models diverge at higher *TDZ* values. The *TDZ* at which divergence occurs varies inversely with the R_{PZ}. Above this, our model predicts that *TAZ* increases at a lower rate with increasing *TDZ*, which may be attributable to the additional high phytate data that we have used. Whereas more detailed comparison with modeling of the Food and Nutrition Board data (7) was not possible because phytate data were not available, we did use the model to predict the phytate intake of the those subjects. The model predicted a mean *TDP* of 0.45 mmol/d and a resulting R_{PZ} of 3.1. This is consistent with the fact that the Food and Nutrition Board data were selected from studies of very low phytate diets.

We have shown several variations of the model to accommodate the use of fractional absorption, *FAZ*, or the phytate:-zinc molar ratio, R_{PZ}. Although they add flexibility for the model's predictive applications, these forms of the model are not as well suited for fitting to data, because *FAZ* and R_{PZ} are both ratios of the more fundamental variables, i.e. $FAZ = TAZ/TDZ$ and $R_{PZ} = TDP/TDZ$. In the case of *FAZ*, because there is a correlation between *TDZ* and *TAZ* ($r = 0.73$, $P = 0.0002$), the relation between *FAZ* and *TDZ* is not as strong as that between *TAZ* and *TDZ*. This is manifest in our use of Equation 12 to fit the data. Although producing similar parameter estimates, the goodness if fit was notably inferior. The recommendation to relate zinc absorption to dietary component quantities rather than ratios has been made previously, although based on somewhat different considerations (4). The use of Equation 14, with the passive absorption parameter, to analyze these limited data is a good example of overparameterization, as evidenced by the very wide CI for all parameters. It is noteworthy that the goodness of fit was not improved with the added parameter, apparently indicating that these data do not exhibit evidence of passive absorption. Additional data will be required to discern the existence of passive absorption and demonstrate the usefulness of this version of the model.

In conclusion, we have developed a mathematical model of zinc absorption from a basic conception of the relevant intestinal biochemistry and fit it to selected existing data. Evaluation of the fit finds it to be good and in compliance with regression assumptions, thereby supporting the validity of the model. Evaluation of the parameter estimates and model predictions are also supportive of the model's validity. We judge the model to be well founded, with immediate relevance and applicability to the study of zinc nutrition and metabolism and the estimation of dietary zinc requirements in varied populations. Furthermore, we anticipate the model's evolution and improvement as new data are analyzed and further knowledge of the absorption process incorporated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

A_{MAX}
maximum absorption

FAZ
fractional absorption of zinc

IZiNCG
International Zinc Nutrition Consultative Group

K_P
: equilibrium dissociation constant of zinc-phytate binding reaction

K_{P1}
: association rate constant of zinc-phytate binding reaction

K_{P2}
: dissociation rate constant of zinc-phytate binding reaction

K_R
: equilibrium dissociation constant of zinc-receptor binding reaction

K_{R1}
: association rate constant of zinc-receptor binding reaction

NMA
: passive (nonmediated) absorption coefficient

R_{PZ}, phytate
: zinc molar ratio

TAZ
: total daily absorbed zinc

TDP
: total daily dietary phytate

TDZ
: total daily dietary zinc

ZnP
: zinc-phytate complex

ZnR
: zinc-receptor complex

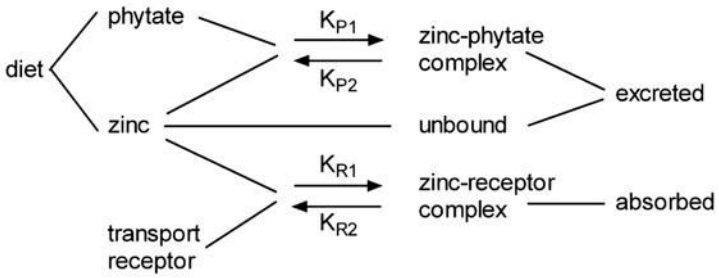

Figure 1.

A rudimentary conception of interactions between transport receptors, dietary zinc, and dietary phytate in the intestinal lumen. K_{P1}, K_{P2}, K_{R1}, and K_{R2} are association and dissociation constants of the binding reactions. This conception forms the basis of the mathematical model.

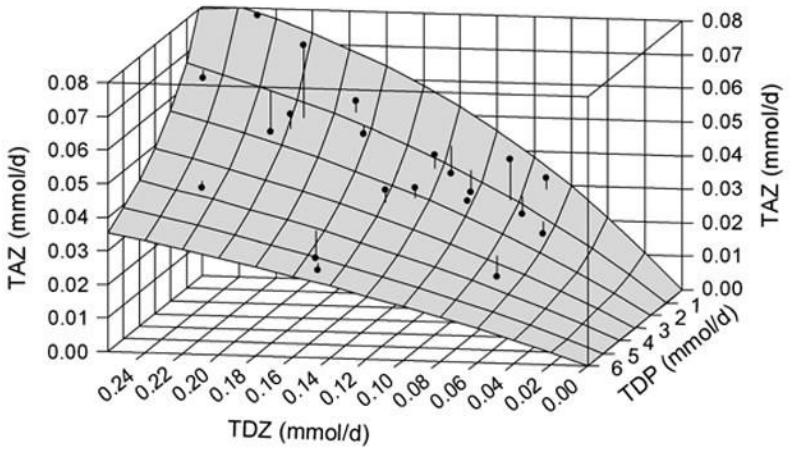

Figure 2.

Three-dimensional plot of the data (●) and the model (gray surface) fit to the data. The vertical stem extending up or down from each datum to the surface shows the deviation of the datum from the model, i.e. the residual. The model is extrapolated to 0 TDZ to demonstrate the behavior of the model at low TDZ. The origin (0,0,0) is positioned at the right rear to make the graph more visually informative. All variables are in units of millimoles per day.

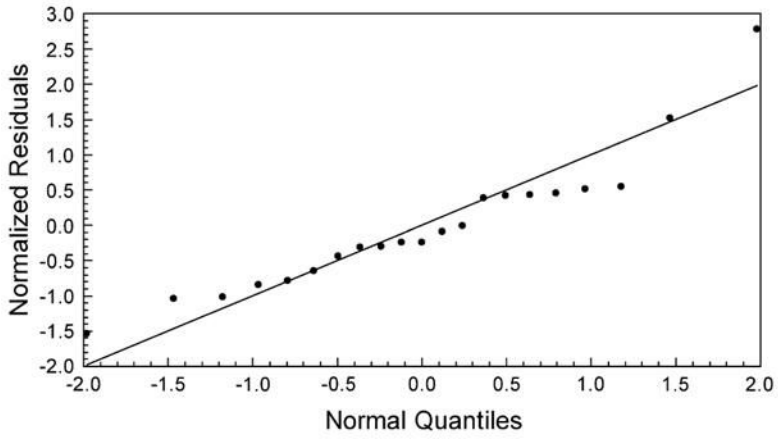

Figure 3.

The normal probability plot of the residuals from fitting the model. A normal distribution is evidenced by the points roughly lying on a straight line. The plot demonstrates adequate normality of the residuals. A normal distribution is more evident when the discrepant high datum (upper right) is removed from the analysis.

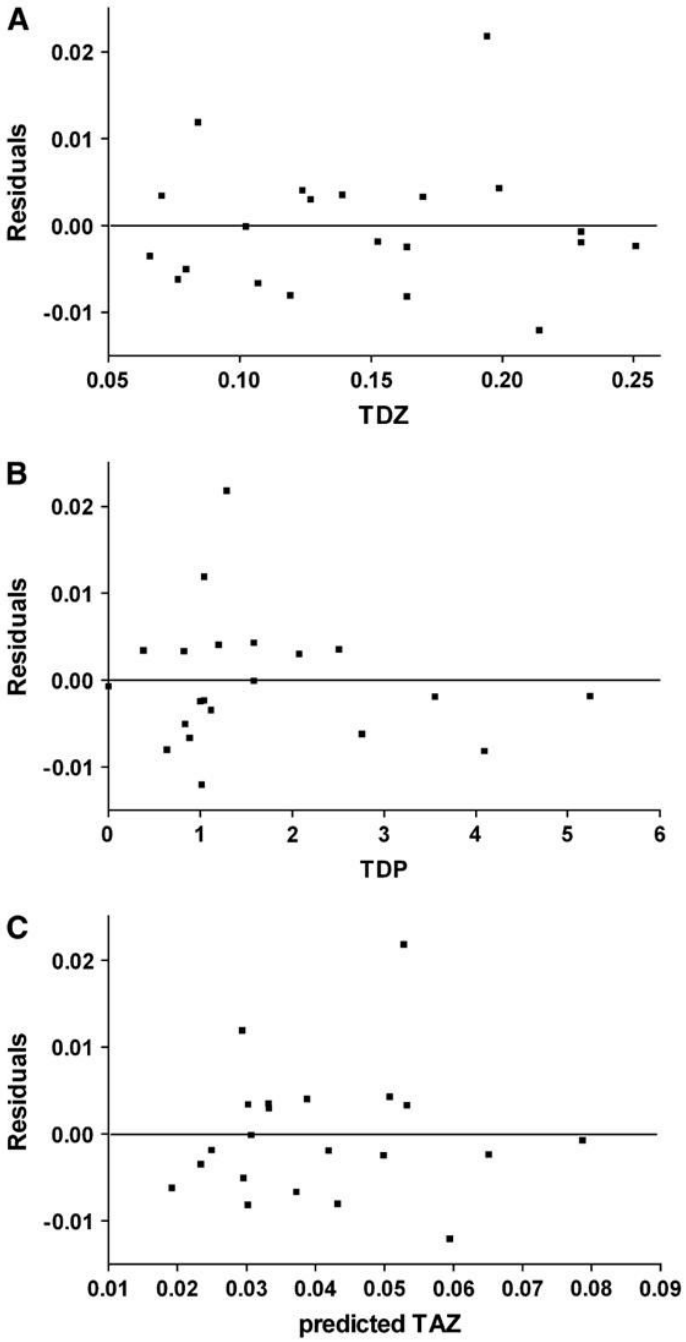

Figure 4.
Residuals from the model compared with (*A*) TDZ, (*B*) TDP, and (*C*) predicted TAZ. The residuals exhibited no clear evidence of nonconstant variance. Furthermore, no discernable relation was observed between the residuals and any of these variables.

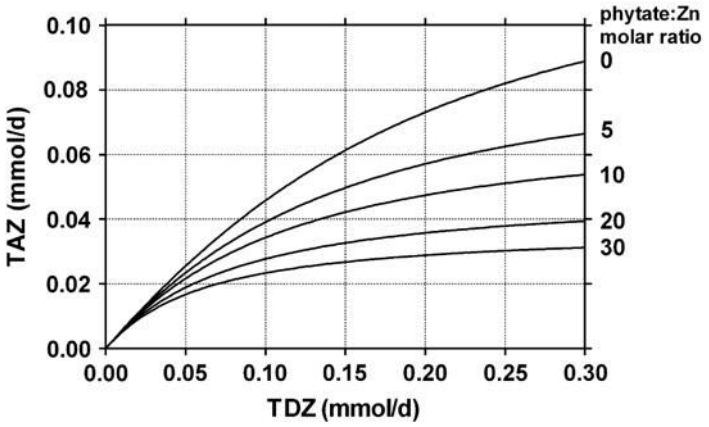

Figure 5.
Curves showing TAZ predicted by the model vs. TDZ for selected phytate:zinc molar ratios between 0 and 30.