Zinc Requirements: Assessment and Population Needs

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Abstract

Reliable estimates of zinc requirements have assumed greater priority as the global public health importance of preventing zinc deficiency has gained increasing recognition. On a global public health basis, our first most evident goal is reliable estimates of average population requirements. Despite expectations of rapid advances towards simpler and more sophisticated strategies, estimations of zinc requirements continue to depend on a factorial approach. Since the Dietary Reference Intakes (DRIs) were published, there have been important advances in techniques for the factorial approach but also confusion resulting from the subsequent publication of conflicting ‘international’ estimates. The reasons for these differences have now been fully elucidated, removing an obstruction to continuing progress and refinements of our knowledge base. A key advance has been the development and validation of a model that can be simply applied to determine the inhibitory effects of phytate on zinc absorption. Better understanding of maternal and young child zinc requirements continues to present a challenge of special importance.

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Introduction

Zinc deficiency now has an established place among the small group of micronutrient deficiencies having acknowledged public health importance of global dimensions. This recognition has underscored the need for reliable, broadly accepted estimates of dietary needs for all population groups consuming a broad variety of diets. Though there have been expectations for some years of new successful approaches for the assessment of zinc requirements, perhaps especially, zinc status-related changes in one or more of the zinc absorption transporter proteins or corresponding mRNA, these have yet to be validated. A factorial approach, therefore, remains not only the strategy of choice but the
only available method. Fortunately, though data remain limited, new concepts and effective modeling over the past decade have resulted in quite fundamental advances in the effectiveness of the factorial approach. The specifics and implications of these advances as well as the resolution of conflicting estimates are the focus of this review. Though a principal focus of this workshop is on development, this paper will be directed to adult requirements. Reliable estimates for all women of child-bearing age are important for the in utero development of their offspring. Estimates of zinc requirements for young children depend primarily on extrapolation from adult estimates. Therefore, reliable estimates of adult zinc requirements provide an essential cornerstone for understanding requirements during all stages of development. These are also an essential starting point for our understanding of the effects of inflammation and chronic/recurrent disease on zinc requirements.

The factorial estimation of average zinc requirements of populations depends on reliable data that can best be considered under three major headings. These are: (1) physiological requirements (PR) defined as the quantity of zinc absorbed daily (TAZ) that is just adequate to match inevitable excretion of endogenous zinc by all routes together with any zinc retention required for new tissue (fig. 1); (2) the estimated average daily zinc requirement (EAR) of bioavailable zinc necessary to achieve absorption of the PR, and (3) the bioavailability of the ingested zinc which is determined at least primarily by the quantity of dietary phytate ingested. This paper will review each of these aspects including the resolution of recent disparities in estimates of zinc requirements. The accurate determination of zinc absorption requires measurement over a period...
of a minimum of one day rather than single meal studies, and all data covered in this review are expressed in terms of mg Zn/day.

**Physiological Requirements**

Typically, except during early lactation, the intestine is the major route of excretion. The quantity of zinc excreted via this route is regulated in response to current zinc absorption and to an undefined but probably limited extent by ‘zinc status’. Other routes of excretion of endogenous zinc are via the kidneys (also regulated but with relatively minor implications for requirements), reproductive system, integument, and, during lactation, the mammary gland. The demands of new tissue add to the PR during childhood and pregnancy, though these may be offset during pregnancy, as may the extra excretion of zinc via the mammary gland, by up-regulation of absorption [1, 2] and, possibly, by down-regulation of endogenous zinc excreted via the intestine [1].

A limitation in concept of human zinc homeostasis in one case and errors in determining the relationship between endogenous fecal zinc (EFZ) and TAZ in another resulted in mistaken estimates of PR in two of three relatively recent publications considered in this review, each of which has had and continues to have an impact globally. In the first of these, in 1996 [3], it was concluded, during this initial (and notable) endeavor to provide a strong evidence base for zinc requirements, that EFZ and, to a small extent, urine varied with adaptation to recent intake or/and ‘status’. This led to the concept of ‘basal’ (fully adapted) and ‘normative’ (non-adapted) PR. However, in both cases these levels were based on low zinc intakes and were regarded as ‘static’ numbers which did not increase with increasing absorption of zinc. This resulted in extremely low and erroneous estimates of PR [4] in what was otherwise an outstanding contribution to the evolution of emphasis on an evidence base for assessing zinc requirements.

A key advance was contributed by the Institute of Medicine (IOM) in 2001 [5] with recognition of the occurrence and significance of a strong positive correlation for EFZ versus the quantity of TAZ which, importantly, was apparent at levels of TAZ well below the PR [6]. The implication is that regulation of EFZ is imperfect, as zinc excretion increases with increasing TAZ when the latter is still below that needed to meet physiologic requirements. This concept and supporting data resulted in estimates of PR for adult males [5] that were more than threefold those estimated by the WHO [3]. The validity of this approach has not been questioned, though relatively minor numerical adjustments are likely as the current limited data base is enlarged, especially with studies of zinc homeostasis while ingesting habitual diets.

Publication of the IOM estimates [5] was followed 3 years later by ‘international’ estimates [7]. It should be noted that these ‘international’ estimates
were based on studies of human zinc homeostasis in the USA or UK with one study of ours in China [8] being the only exception. Two errors in these estimates, both related to the determination of the relationship between EFZ and TAZ, were primarily responsible for major underestimates of PR [9]. Because these estimates have been widely disseminated and utilized globally, they have been the cause of much confusion and have inhibited progress in our quantitative understanding of zinc homeostasis and requirements for several years. Correction of these errors together with using the same reference data for adult size and correction of an IOM overestimate of menstrual zinc losses results in close reconciliation [9]. The very small residual differences (fig. 2–4) are attributable to the use of different datasets, notably with IOM utilizing male data only to define the relationship between EFZ and TAZ [5] and International Zinc Nutrition Consultative Group (IZiNCG) [7] using data from both genders. The closeness of the reconciliation is remarkable in view of the limited database, the interpretation of which remains complex for females [10] and the range of laboratory techniques and strategies that have been used.

Fig. 2. Discrepancies between adult PR for zinc estimated by the IOM in 2001 [5] and IZiNCG in 2004 [7].
Estimated Average Zinc Requirements for Populations

The EAR is determined from the intercept between the PR and the model describing the relationship between TAZ and ingestion of bioavailable zinc. The conceptual advance that has occurred subsequent to the publication of the DRIs by the IOM is that this relationship is best fit by a saturation response model [4]. This is not surprising as the absorption of zinc by the enterocyte has long been known to be a saturable process in mammals [11]. Recognition of the appropriateness of this model has not only provided the best fit for data, but has proved a major visual advance in our understanding of human zinc homeostasis including advancing our understanding of the relationship between the quantity of bioavailable zinc ingested and the efficiency of zinc absorption. As with the regulation of EFZ, it is apparent that the regulation of zinc absorption is not a completely efficient phenomenon [4] (fig. 5). If it were, the model would coincide with the line of equality between dietary zinc and TAZ until the PR is met and then remain horizontal. The gap between the line of equality and the saturation response model is consistent with the abundant evidence that human

Fig. 3. Residual discrepancies in estimates of PR for zinc after correction of identified errors in estimates.
zinc deficiency, from the very mild to severe, does indeed occur and is no surprise. As up- and down-regulation of proteins involved with zinc absorption via the enterocyte occurs within a short time span, it is concluded that the less than perfect efficiency of absorption at levels of ingestion of bioavailable zinc less than EAR occurs despite maximal up-regulation of transporters and other proteins involved with zinc absorption. Despite this limitation on adaptation, fractional absorption is quite favorable at levels of ingestion less than EAR, averaging approximately 40%. It is noted that the estimated average requirement approximates half maximal absorption of zinc, below which absorption is relatively favorable. Also of note is the low and increasingly poor fractional absorption of zinc when ingestion of bioavailable zinc exceeds the estimated average requirement.

While search continues for the ‘holy grail’ of a sensitive, reliable biomarker of zinc status, we should not underrate, especially at the population level, how much we can learn about status from reliable determinations of dietary zinc intakes and, from there, the percentage of the population with zinc intakes

**Fig. 4.** Effect of selection of different adult weight reference standards in estimating excretion of endogenous zinc via the integument. Minor residual differences between estimates attributable to use of different datasets.
below the EAR [12]. The only substantial additional information required is the bioavailability of the ingested zinc, a topic to be addressed in the next section. For the individual, biomarkers are certainly needed as is adequate information to provide a reliable measure of the variance around the EAR.

**Bioavailability**

Phytate is the one dietary factor recognized to have a major effect on the absorption of ingested zinc apart from the quantity of ingested zinc itself. The inhibitory effect of phytate on zinc bioavailability is notable and of most profound importance in populations largely dependent on plant products, especially unrefined cereal grains and beans. In developing the DRIs for zinc, the IOM concluded that, at that time, there were insufficient data to reliably estimate the quantitative effect of phytate on daily absorption of zinc. Subsequent trivariate modeling of TAZ as a function of both daily zinc and daily phytate intake appears to have quite successfully addressed the estimation of the quantitative effect of different quantities of dietary phytate on zinc absorption [13] over the spectrum of intake of dietary zinc. Though minor modifications of this model remain in progress as the effects of other dietary components are examined, the quality of both the parameter estimates and fit of the model to the data are reassuring. Moreover, it has been validated independently [14]. Based on this

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**Fig. 5.** Estimates of daily requirements for ingested zinc for adult males. A: line of equality between ingested zinc and absorbed zinc; B: saturation response curve fitted to adult male data utilized by IOM [5]; C: predicted effect of 1 mmol of daily dietary phytate. Vertical lines from intercept of estimated PR and saturation response curves indicate estimated average requirements for ingested zinc. Adapted from Hambidge et al. [17].
model, the effect of realistic quantities of dietary phytate on estimated requirements of ingested zinc necessary to meet physiological zinc requirements in adults is illustrated in figure 5. This model has been used, for example, to predict the level of enhanced zinc absorption achieved by zinc biofortification of wheat [15]. It is apparent that existing and future strategies to reduce the phytate content of meals prior to consumption, without equivalent reductions in zinc, can have a profound effect on zinc requirements and the prevalence of zinc deficiency in populations dependent on high-phytate diets.

Infants and Children

Data on zinc homeostasis in infants and young children, the most vulnerable to the effects of zinc deficiency, are limited. It is known that the same saturation response modeling as for adults serves to fit existing experimental data well [16]. In line with lower physiological zinc requirements, the models have lower levels of absorbed zinc and lower estimates of maximal zinc absorption [16, 17]. It has been noted that if these models, even for premature infants, are adjusted for differences in length of small intestine, they fit closely with the adult model [16]. However, direct measurements of the inhibitory effect of phytate in young children remain pending at this time, and measurements of endogenous zinc losses are limited.

Conclusions

At least 15 years ago, there was a perception that stable isotopic investigations were outdated, almost before their application had begun and long before we knew how to use them optimally in estimating zinc requirements. There was a palpable feeling that molecular techniques, in particular, would sweep all before them. In fact, we need these ‘out-of-date’ techniques more than ever and depend on them to estimate zinc requirements with reasonable precision. However, the necessary data are still remarkably limited, and the variance remains uncertain. Moreover, existing data continue to be evaluated, and it is apparent that additional modifications of current understanding of human zinc homeostasis and requirements will follow [Miller et al., unpubl.]. This underlines the importance of building onto an existing base that is as reliable as current data permit.

The greatest challenge is presented by those for whom we need it most. At this time, we still depend to a very large extent on extrapolation from adults to estimate zinc requirements in young children. Maternal estimates are complicated by changes in zinc homeostasis that include regulation of absorption and probably of intestinal excretion of endogenous zinc and, during the entire course of pregnancy, by the interrelationships between the maternal, placental and fetal regulation of zinc homeostasis.
References


