The Need for Food Fortification With Zinc in India: Is There Evidence for This?

RAGHU PULLAKHANDAM,[1] BHARATI KULKARNI,[2] ANURA V KURPAD,[3] HARSHPAL S SACHDEV[4]
[1]ICMR-National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, Telangana.
[2]Division of Reproductive, Child Health & Nutrition, Indian Council of Medical Research, New Delhi.
[3]St John's Medical College, Bengaluru, Karnataka.
[4]Sitaram Bhartia Institute of Science and Research, New Delhi.
Correspondence to: Dr Raghu Pullakhandam, Drug Safety Division, ICMR-National Institute of Nutrition, Jamai Osmania, Hyderabad, Telangana 500007. raghu_nin2000@yahoo.com

There has been recent advocacy for food fortification with zinc in India. However, there are three important conditions that should be established before fortifying food with any micronutrient, which requires that there should be *i*) Established high prevalence of biochemical or sub-clinical deficiency (≥20%), *ii*) Low dietary intakes that increase the risk of deficiency, and *iii*) Evidence of efficacy of supplementation from clinical trials. For zinc, all three conditions are not satisfied. The prevalence of low serum zinc concentrations in Indian children is well below 20% (~6%), signifying that zinc deficiency is not a public health problem. There is no risk of dietary zinc inadequacy in Indian populations where intake has been measured. Finally, there is no robust evidence that zinc-fortified foods improve functional outcomes, even if the serum zinc concentration is increased. Thus, contemporary evidence does not justify the need for food fortification with zinc in India.

Keywords: *Deficiency, Intake, Supplementation*.

Published online: April 20, 2023; **PII**: S097475591600527

Zinc is an essential nutrient for growth [1-3]. Whole-body zinc content is stable over a wide range of dietary zinc intakes indicating its efficient homeostasis [2,3]. Zinc absorption takes place throughout the small intestine, but the duodenum contributes maximally to zinc absorption owing to the higher zinc concentration in the duodenal lumen after a meal [2,3]. Excess endogenous zinc is excreted in feces via pancreatic secretions. The balance of intestinal absorption and endogenous fecal zinc (EFZ) excretion are two important factors for zinc homeostasis [3]. During zinc deficiency, EFZ decreases, with a concurrent increase in intestinal absorption. On the other hand, during an excess zinc intake, EFZ increases while its absorption remains unaffected.

Physiologically, zinc is defined as a type 2 nutrient. During deficiency, its functional pools are maintained at the expense of growth, but severe dietary restriction (<1 mg/day) results in reduced concentrations in functional tissue pools, with clinical symptoms such as growth faltering and infectious morbidity [3]. Thus, except when serum zinc concentration (SZC) is reduced during severe dietary zinc restriction, there are no biomarkers of mild or subclinical zinc deficiency (like serum ferritin for iron deficiency). Therefore, other contextual deficiency indicators, such as dietary zinc inadequacy and the prevalence of stunting, are suggested for assessing the risk of zinc deficiency in populations [1,2].

As severe forms of malnutrition have reduced substantially in India over the years, the focus has shifted to finding and preventing subclinical micronutrient deficiencies, with potential deficits in functionality (growth, cognition, etc). This subclinical deficiency can be assessed by measuring either blood biomarkers or risk of inadequacy in dietary intake, with prevention by diverse dietary intakes and through suitable public health interventions. The World Health Organization (WHO) has suggested staple food fortification with micronutrients as a short-term approach to increase micronutrient intakes [4], as it is potentially sustainable, does not require behavioral modifications, and is relatively safer and cost-effective compared to therapeutic supplementation [4]. However, the WHO suggested documenting important information for introducing specific fortification programs. These were: *i*) Established high prevalence of biochemical or subclinical deficiency (≥20%), *ii*) Low dietary intakes that increase the risk of deficiency, and *iii*) Fortification will produce a health benefit [4].

We review these three core conditions from the Indian perspective, and highlight uncertainties that have direct implications for considering zinc fortification as a public health strategy. Additional considerations in the evidence to decision framework are beyond the scope of detailed examination. These include adverse effects, user perspective (values and acceptability), feasibility, resource requirements, and cost-effectiveness [5].

ASSESSMENT OF ZINC STATUS

The serum or plasma zinc concentration, collectively referred to as SZC subsequently, is the usual biomarker for assessment of zinc status, or elevated risk of zinc deficiency, in populations [1,2]. Although zinc intakes are not associated with SZC in the American population [6], possibly due to a ceiling effect, where at higher intakes the SZC response is blunted, a systematic review [7] indicates that doubling the zinc intake results in ~9% increase in SZC, and therefore, the SZC can reflect the zinc intake.

Age, gender, and fasting status specific SZC cutoffs are suggested by International Zinc Nutrition Consultative Group (IZiNCG) to assess the risk of zinc deficiency in populations derived from National Health and Nutrition Examination Survey (NHANES)-II [1]. These cutoffs are statistically derived as the 2.5th centile from the SZC distribution in the US population (**Table I**), and used in many countries, including India. Experimentally, severe zinc restriction (<1mg/day for 2-9 weeks) in human volunteers has shown a progressive and rapid fall in SZC, with the onset of non-specific clinical symptoms [8]. Zinc supplementation rapidly improved the SZC and resolved these clinical signs. In Receiver Operating Characteristic (ROC) analyses to derive a diagnostic cutoff of zinc deficiency, the highest specificity was observed at a cutoff SZC value of 70 µg/dL. This value was similar to the statistically defined IZiNCG adult cut-off, suggesting that the latter remains useful [8].

Using statistical methods identical to IZiNCG [1], SZC cutoffs for apparently healthy 1-19-year-old children and adolescents (selected after applying more stringent exclusion criteria) were recently reported [9]. Interestingly, these cutoffs were lower (by 10-18 µg/dL) than those of the IZiNCG. There could be several reasons for this. First, the SZC cutoffs are variable and depend on the statistical distribution of SZC they are derived from. The cutoffs derived from the recent NHANES (2011-14) data are lower than the IZiNCG value (66 vs 74 µg/dL). Second, the dietary intakes of the NHANES reference population were almost twice that of their requirements, resulting in a right shift of the SZC distribution with higher 2.5th centile cutoffs. Third, the lower Indian cutoff, without any functional deficit, could indicate a successful adaptation to low bioavailable dietary zinc. Fourth, there could be differences in body composition, particularly lower lean body mass in Indians [9]. Thus, a range of SZC that are compatible with good health exist, and local contextualization of these values is critical when assessing the risk of zinc deficiency.

Inflammation is a critical confounder, left-skewing the SZC distribution independent of zinc status. Isolated Indian studies have reported 25-50% prevalence of low SZC [10], but the majority did not adjust for underlying inflammation, which overestimated zinc deficiency prevalence. The Comprehensive National Nutrition Survey (CNNS, 2016-2018), which surveyed children across India, provided representative data on SZC values (along with measurement of inflammation by serum C-reactive protein concentration) in Indian children and adolescents. The inflammation-adjusted pre-valence of low SZC (or zinc deficiency), using the IZiNCG cutoffs, among preschool (17.4%) and school-age (15.8%) children was below 20%, meaning that zinc deficiency was not a public health problem in these age groups. In adolescents, the prevalence of zinc deficiency was higher at 31% [10]. However, when India-specific SZC cutoffs were used, the national prevalence of zinc deficiency was ≤6% among 1-19-year children and adolescents, and this was less than 20% across all geographic states [9].

Another indirect, distal indicator considered for assessing zinc deficiency is the prevalence of stunting [1]. However, stunting is multifactorial in origin and SZCs are not associated with height for age in Indian children [9], and zinc supplementation in settings with high prevalence of stunting was not associated with improvements [11]. Indeed, in a high income European country, the prevalence of low SZC was 31%, when the prevalence of stunting was

Table I India-specific and IZiNCG Cutoffs to Define Low Serum Zinc Concentration (SZC) and Prevalence Estimates of Low SZC in Indian Children and Adolescents (Aged 1-19 Year)

Age	*Gender*	*Serum zinc concentration*						
		India- specific cutoff[a]			*IZiNCG cutoffs*[b]			
		Morning fasting	*Morning non-fasting*	*Prevalence*[a] *(%)*	*Morning fasting*	*Morning non-fasting*	*After noon*	*Prevalence*[a] *(%)*
<10 y	Both	56	55	<5 y: 6.0 5-9 y: 5.7	-	65	57	<5 y: 17.4 5-9 y: 15.8
>10 y	Female	54	53	5.6	70	66	59	31.1
	Male	56	55		74	70	61	

All values in µg/dL. [a]*Pullakhandam, et al. 2022 [9] and Pullakhandam, et al. 2021 [10].* [b]*IZiNCG, Food Nutr Bull. 2004 [1].*

just 1% [12]. Therefore, the use of stunting as an indicator in assessing zinc deficiency is not valid, and controversial.

ZINC REQUIREMENTS AND INTAKES IN INDIA

Assessing the dietary zinc intakes *vis-à-vis* their requirement is a critical component of quantifying the risk of zinc deficiency [13], as SZCs are not a robust diagnostic of mild deficiency [1,2]. This exercise requires data on both nutrient requirements and dietary intake.

The nutrient requirements of Indians, published by the Indian Council of Medical Research (ICMR) in 2020 [13], provided three important metrics of the zinc requirement (**Table II**) viz., the estimated average requirement (EAR, average population requirement), the recommended dietary allowance (RDA, 97.5% of the population will have a requirement less than this) and the tolerable upper level of intake (TUL, the intake at which the risk of adverse effects starts). The EAR is factorially computed, considering factors such as daily loss of zinc (EFZ, urine, sweat, semen and menstrual losses), losses due to lactation, and sequestration during tissue accretion in growing children and during pregnancy. The daily replacement of these combined daily losses are adjusted for by dietary bioavailability, to derive the final dietary requirement [13].

As explained above, EFZ loss and bioavailability are two most important factors in this requirement. Added to this complexity is the homeostatic adjustment of EFZ, influenced by both recent intake (absorbed zinc) and body status. Stable isotopic methods now allow the precise measurement of EFZ as well as fractional zinc absorption [2]. Therefore, in India [15], the combined excretion of zinc from all possible routes was regressed against absorbed zinc, to find the minimum amount of absorbed zinc that was required to match losses. This was then adjusted for bioavailability to derive the EAR. A coefficient of variation of EAR of 10% was assumed to derive the RDA, while the TUL value was adopted from the Institute of Medicine recommendation [14]. Still, more contextual data on EFZ excretion are required, with low zinc-density and high phytic acid cereal/pulse diets.

Table II Age- and Gender-based ICMR, 2020 Zinc Requirements and Tolerable Upper Intakes for Indians

Category/age	*ICMR, 2020 (mg/d)*		
	EAR	*RDA*	*TUL*
Men	14.1	17	40
Women[a]	11.0	13.2	40
Children			
7-12 mo	2.1	2.5	5
1-3 y	2.8	3.3	7
4-6 y	3.7	4.5	12
7-9 y	4.9	5.9	12
Adolescents[b]			
Boys 10-12 y	7.0	8.5	23
Girls 10-12 y	7.1	8.5	23
Boys 13-15 y	11.9	14.3	34
Girls 13-15 y	10.7	12.8	34
Boys 16-17 y	14.7	17.6	34
Girls 16-17 y	11.8	14.2	34

EAR: estimated average requirement; RDA: recommended dietary allowance (Indian Council of Medical research, 2020) [13]; TUL: tolerable upper intake (Institute of Medicine, 2021) [14]. [a]Women of reproductive age; [b]TUL for 9-13 year age group is 23 mg/d.

Next, the dietary inadequacy assessment requires representative dietary zinc intake data. This allows estimation of the risk of intake inadequacy as the proportion of population intakes below the EAR (by the EAR cut point method) or the probability of inadequacy against the entire requirement distribution [2,13]. Based on probability theory, this proportion is ≤50% in a normal population [15]. However, there is lack of good quality national dietary intake data in India. The IZiNCG categorized India as a high-risk country for zinc deficiency based on (in addition to stunting) inadequate absorbable zinc intakes (26%) that were derived from FAO food balance sheets [1]. Trends (from 1983 to 2012) from National Sample Survey Organization (NSSO) data indicate that prevalence of inadequate zinc intake has increased from 17.1%-24.6% between 1983 and 2012 [16]. However, it should be noted that these analyses were based on either food balance sheets or per capita household food purchases, with imputed intakes from other settings, and the absorbable zinc was based on estimated phytate/zinc molar ratios. Therefore, further confirmation of dietary assessment with representative and accurate dietary intake data across all physiological, gender groups and demographics is sorely needed to identify the potential variables linked with risk of dietary zinc inadequacy, verified with simultaneous SZC data. However, even in these analyses the dietary zinc inadequacy remained ~25%, implying that the intakes in 75% of the population are above the EARs.

EFFICACY OF ZINC SUPPLEMENTATION/FORTIFICATION

Most studies of zinc supplementation/fortification have investigated increments in SZCs, linear growth, diarrhea and morbidity. There is robust evidence that oral zinc therapy reduces the severity of diarrhea in children, and India has pioneered evidence in this regard [17-20]. Further, preventive zinc supplementation (≥10 mg) also reduced the incidence of diarrhea and pneumonia, and tended to reduce related mortalities [21,22]. Molecular evidence indicates that an ionic imbalance (Na^+ and Cl^- loss) enforces water loss during diarrhea, which can be offset by zinc via cAMP signaling mechanisms [23], and that zinc may also inhibit viral replication [2]. However, on anthropometric indicators (stunting, underweight or wasting), zinc supplementation (mean dose ≥7.5 mg/day) had either modest or no effect, even in LMICs considered to be at high risk of zinc defeciency [11,24,25]. It is worth noting that the doses used in the majority of these studies were greater than 10 mg (2-3 times higher than EAR of under-five children, and higher than the TUL). Further, the effects of zinc on intestinal function in animal models appear to be independent of zinc status [2]. Therefore, while therapeutic zinc supplementation as adjunct therapy for diarrhea as recommended by WHO/UNICEF is beneficial, preventive zinc supplementation with pharmacological doses of zinc to improve growth or reduce morbidity does not appear to be ideal, in context of the lack of impact of supplementation on anthropometric indicators [26].

Systematic reviews of zinc fortification trials (zinc alone or with other micronutrients) have shown a significant increase in SZCs or reduction in prevalence of low SZCs [27-29], where the effect was higher with zinc-alone fortification compared to when it was combined with other micronutrients [28]. However, this was the sole effect, with no reported evidence on improvements in any functional outcome (incidence of diarrhea and morbidity, or anthropometry). One review reported a significant weight gain (of 0.4kg), but explicitly stated that this effect could not be directly attributed to zinc [28]. That most zinc fortification studies are conducted in LMICs, and yet there is no evidence of functional benefits, suggests that either there is no risk of zinc deficiency or that zinc fortification is ineffective in improving linear growth.

EVIDENCE FOR ZINC FORTIFICATION IN INDIA

The important question one must ask is what is the desired goal of zinc fortification of foods in India – is it solely to improve SZC or to confer functional benefits such as reduced stunting, reduced diarrhea and other morbidities? As discussed above, SZCs are not the definitive indicators of zinc deficiency, and need to be supported by other indicators. Nevertheless, the SZC cutoffs for zinc deficiency in healthy Indian children are lower than that recommended by IZiNCG, and yield a prevalence of zinc deficiency of ~6%. Thus, in Indian children, it appears that zinc deficiency is not a public health concern. It is then logical to evaluate if target functional outcomes were improved with zinc fortification. Zinc fortification trials have not shown definitive improvements in anthropometric outcomes (like stunting) or reduced diarrheal incidence in children. There is also increasing clinical and basic evidence that the mode of action of zinc supplementation in diarrhea and other morbidities could be pharmacological. Clearly, there is no strong evidence to support zinc fortification of foods yet in India, unless the target is solely to improve the SZCs, or to chase a mirage of functional benefits, which ironically, are not achieved even at therapeutic doses. Further, available estimates of the prevalence of dietary inadequacy data suggest no dietary deficiency, but more detailed data would be helpful, particularly to evaluate risks of exceeding the TUL in the event of fortification or supplementation. For example, an Ethiopian simulation study reported that zinc fortification (providing 4.1 mg zinc/day) significantly reduced dietary inadequacy but increased the risk of exceeding the TUL by 50% among young children [30]. A final important consideration is that once fortification is implemented, it reaches all sections of the population, including men, pregnant women, elderly, and persons with chronic disease. The intended functional outcome in these population sections should be stated, along with risk/benefit analyses, before decisions on universal zinc food fortification are taken.

Contributors: All authors conceived the idea; PR drafted the manuscript; AK, HSS and BK reviewed it critically. All authors approved the final version of manuscript, and are accountable for all aspects related to the manuscript.
Funding: None; *Competing interests*: None stated.
Note: AVK and HSS are presently members of the FSSAI Scientific Committees and ICMR Committee to set Nutrient Requirements of Indians. The views expressed by the authors here are their personal, and do not reflect the views of the institutions or committees that the authors are affiliated to.

REFERENCES

1. International Zinc Nutrition Consultative Group, Brown KH, Rivera JA, et al. International Zinc Nutrition Consultative Group (IZiNCG) technical document #1. Assessment of the risk of zinc deficiency in populations and options for its control. Food Nutr Bull. 2004;25:S99-203.
2. King JC, Brown KH, Gibson RS, et al. Biomarkers of nutrition for development (BOND)-zinc review. J Nutr. 2015;146: 858s-85s.
3. King JC, Shames DM, Woodhouse LR. Zinc homeostasis in humans. J Nutr. 2000;130:1360S-6S.
4. Dary O, Hurrell R. Guidelines on food fortification with micronutrients. World Health Organization, Food and Agricultural Organization of the United Nations,. 2006. P. 1-376.
5. World Health Organization. WHO handbook for guideline development. 2nd ed ed. Geneva: World Health Organization, 2014.
6. Hennigar SR, Lieberman HR, Fulgoni VL 3rd, McClung JP. Serum zinc concentrations in the US population are related to sex, age, and time of blood draw but not dietary or supplemental zinc. J Nutr. 2018;148:1341-51.
7. Moran VH, Stammers AL, Medina MW, et al. The relationship between zinc intake and serum/plasma zinc concentration in children: A systematic review and dose-response meta-analysis. Nutrients. 2012;4:841-58.
8. Wessells KR, King JC, Brown KH. Development of a plasma zinc concentration cutoff to identify individuals with severe zinc deficiency based on results from adults undergoing

experimental severe dietary zinc restriction and individuals with acrodermatitis enteropathica. Nutr. 2014;144:1204-10.

9. Pullakhandam R, Ghosh S, Kulkarni B, et al. Reference cut-offs to define low serum zinc concentrations in healthy 1-19 year old Indian children and adolescents. Eur J Clin Nutr. 2022; 76:1150-7.
10. Pullakhandam R, Agrawal PK, Peter R, et al. Prevalence of low serum zinc concentrations in Indian children and adolescents: findings from the Comprehensive National Nutrition Survey 2016-18. Am J Clin Nutr. 2021;114:638-48.
11. Gera T, Shah D, Sachdev HS. Zinc supplementation for promoting growth in children under 5 years of age in low- and middle-income countries: A systematic review. Indian Pediatr. 2019;56:391-406.
12. Vreugdenhil M, Akkermans MD, van der Merwe LF, et al. Prevalence of zinc deficiency in healthy 1-3-year-old children from three western European countries. Nutrients. 2021;13: 3713.
13. ICMR. Indian Council of Medical Research , National Institute of Nutrition. Nutrient Requirements for Indians. A report of the expert group. Department of Health Research, Ministry of Health and Family Welfare, Government of India. . 2020.
14. Institute of Medicine Panel on M. Dietary reference intakes for vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. National Academies Press, 2001.
15. Ghosh S, Thomas T, Pullakhandam R, et al. A proposed method for defining the required fortification level of micro-nutrients in foods: An example using iron. Eur J Clin Nutr. 2022 Sep 8. Epub ahead of print.
16. Smith MR, DeFries R, Chhatre A, et al. Inadequate zinc intake in India: Past, present, and future. Food Nutr Bull. 2019;40: 26-40.
17. Bhutta Z, Bird S, Black R, et al. Zinc Investigators Collaborative Group. Therapeutic effects of oral zinc in acute and persistent diarroea in children in developing countries: pooled analysis of randomized controlled trials. Am J Clin Nutr. 2000;72:1516-22.
18. Bahl R, Bhandari N, Saksena M, et al. Efficacy of zinc-fortified oral rehydration solution in 6- to 35-month-old children with acute diarrhea. J Pediatr. 2002;141:677-82.
19. Sazawal S, Black R, Bhan M, et al. Effect of zinc supplementation during acute diarrhea on duration and severity of the episode. A community based, doubleblind controlled trial. N Engl J Med. 1995;333:839-44.
20. Bhutta Z, Black RE, Brown K, et al. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. J Pediatr. 1999;135:689-97.
21. Yakoob MY, Theodoratou E, Jabeen A, et al. Preventive zinc supplementation in developing countries: impact on mortality and morbidity due to diarrhea, pneumonia and malaria. BMC Public Health. 2011;11:S23.
22. Rouhani P, Rezaei Kelishadi M, Saneei P. Effect of zinc supplementation on mortality in under 5-year children: A systematic review and meta-analysis of randomized clinical trials. Eur J Nutr. 2022;61:37-54.
23. Canani RB, Buccigrossi V, Passariello A. Mechanisms of action of zinc in acute diarrhea. Current opinion in gastroenterology. 2011;27:8-12.
24. Imdad A, Bhutta ZA. Effect of preventive zinc supplementation on linear growth in children under 5 years of age in developing countries: a meta-analysis of studies for input to the lives saved tool. BMC Pub Health. 2011;11:1-14.
25. Liu E, Pimpin L, Shulkin M, et al. Effect of zinc supplementation on growth outcomes in children under 5 years of age. Nutrients. 2018; 10:377.
26. Radhakrishna KV, Hemalatha R, Geddam JJ, et al. Effectiveness of zinc supplementation to full term normal infants: A community based double blind, randomized, controlled, clinical trial. PLoS one. 2013;8:e61486.
27. Shah D, Sachdev HS, Gera T, et al. Fortification of staple foods with zinc for improving zinc status and other health outcomes in the general population. Cochrane Database Syst Rev. 2016:CD010697.
28. Tsang BL, Holsted E, McDonald CM, et al. Effects of foods fortified with zinc, alone or cofortified with multiple micro-nutrients, on health and functional outcomes: A systematic review and meta-analysis. Adv Nut.. 2021;12:1821-37.
29. Das JK, Kumar R, Salam RA, Bhutta ZA. Systematic review of zinc fortification trials. Ann Nutr Metab. 2013;62:44-56.
30. Abebe Z, Haki GD, Baye K. Simulated effects of home fortification of complementary foods with micronutrient powders on risk of inadequate and excessive intakes in West Gojjam, Ethiopia. Maternal Child Nutr. 2018;14:e12443.