REVIEW ARTICLE

Zinc Deficiency in Humans and its Amelioration

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Abstract

Zinc (Zn) deficiency in humans has recently received considerable attention. Global mortality in children under 5 years of age in 2004 due to Zn deficiency was estimated at 4,53,207 as against 6,66,771 for vitamin A deficiency; 20,854 for iron deficiency and 3,619 for iodine deficiency. In humans 2800-3000 proteins contain Zn prosthetic group and Zn is an integral component of zinc finger prints that regulate DNA transcription. Zinc is a Type-2 nutrient, which means that its concentration in blood does not decrease in proportion of the Zn deficiency. Adverse effects of Zn deficiency vary with age: low weight gain, diarrhoea, aneroxia and neurobehavioral disturbances are observed in infants, while skin changes and dwarfism are frequent in toddlers and adolescents. Common manifestations of Zn deficiency among elderly include hypogeusia, chronic non-healing ulcers and recurrent infections.

Ameliorative measures of Zn deficiency in humans can be classified in two groups, namely, nutraceutical and Bio-fortification of food grains. Nutraceutical interventions include pharmaceutical supplements, dietary supplements and dietary diversification, while Bio-fortification of food grains can be achieved by genetic modification (GM) of crops or by agronomic techniques that include soil or/and foliar fertilization of crops.

The major disadvantage of nutraceutical approaches is that the major beneficiaries are urban people and the poor rural masses that need adequate Zn nutrition most are left out. Genetic Bio-fortification of food grains requires large amounts of funds and a fairly long-period of time. Further, a large number of countries have not yet accepted genetically modified (GM) foods. On the other hand agronomic Bio-fortification of food grains yields immediate effects and rural and urban people are equally benefitted. Our studies have shown that Zn concentration in cereals (rice, wheat etc) and pulses can be considerably increased by soil or/and foliar fertilization of cereal and pulse crops with Zn. Needless to add that cereals and pulses are the major components of a vegetarian human diet in India.

Key Words

Zn denser grains; Zn deficiency symptoms; Zn bio-availability; Phytate; Zn RDA

Introduction

An often cited quotation of Hippocrates, the great Greek physician, philosopher and naturalist, is 'Let food be your medicine and medicine be your food' (via internet). Food has been the main concern of man for his survival since the very day he was created. History tells us that in India as well as in several parts of the world there were millions of deaths, whenever the crops failed and famines occurred (1). Food has always been and probably will continue to be in short supply in one or the other part of the world and since the biennial 1990-92, the number of under-nourished people in the world has always been above 800 million (2). Thanks to 'Green Revolution', India has achieved food security, in general, although protein-energy malnutrition still haunts several parts of India (3). However, we must at this point also think of food quality and nutritional security (4). In addition to protein, carbohydrate and fat, human body needs a large number of micronutrients that include vitamins (5) and minerals. Of the minerals, iodine deficiency leading to goiter (6) and iron deficiency leading to anemia (7) have received considerable attention. Zinc deficiency in humans has recently received attention (8, 9). Black et al. (10) reported that as regards global mortality in children under 5 years of age in 2004, zinc deficiency with a mortality of 4,53,207 was next only to vitamin A deficiency with a mortality of 6,66,771; as compare to this mortalities due to iron and iodine deficiencies were only 20,854 and 3,619, respectively. The geographical regions most affected are Asia (especially Bangladesh and India), Africa and the Western Pacific (11).

Health Problems due to Zinc Deficiency & Toxicity: In humans 2800-3000 proteins contain Zn prosthetic group (12). Zinc is involved in several enzymes (13) and is an integral component of zinc finger prints that regulate DNA transcription (14). Zinc deficiency therefore can lead to several health problems. Adverse health effects due to Zinc deficiency vary with the age and include low weight gain, diarrhea (15, 16) pneumonia (17), neurobehavioral disturbances (18) in fancy; skin changes, dwarfing (19) and conjunctivitis among the toddlers and school children and hypogeusia (impaired taste sensitivity), chronic non-healing ulcers, recurrent infections and visual acuity loss (20) among elderly and adverse pregnancy outcomes in females (21).

Zinc is a 'Type 2' nutrient and its concentration does not decrease in proportion to the degree of deficiency (9). Zinc deficiency is difficult to diagnose, because its manifestations are not specific and there are no specific tests. Zinc plasma level of < 70 µg dl-1 is considered cutoff for zinc deficiency (22). Acute toxicity effects of high zinc intake include nausea, vomiting, loss of appetite, abdominal cramps, diarrhea and headache.

RDA for Zinc and its Bioavailability: RDA (recommended dietary allowance) for zinc varies from 2mg for 0-6 month old infants to 11 mg for 19+ year male adults (Table 1). Table 1 also provides tolerable upper intake values. The US Food and Drug Administration have coined a term daily value (DV), which is 15 mg for adults and children over 4 years. All zinc that is taken in does not become available. Host as well as dietary factors determine bioavailability of zinc. Bioavailability of zinc (BAZ) is more in animal products than in plant products. In plant products phytic acid (inositol hexaphosphate) to zinc ratio (PA:Zn) is considered as the deciding factor for zinc availability. According to WHO (23) PA:Zn ratios of 15 or more, 5-15 and less than 15 are rated as low (10-15% BAZ), moderate (30-35% BAZ) and high (50-55% BAZ). Phytic acid is present in fairly large amounts in cereals, pulses and nuts and this reduces BAZ of zinc present in them (24). BAZ is more in breast milk than in cow's milk (25).

Ways to Alleviate Zinc Deficiency: Broadly there are two ways to alleviate zinc deficiency in humans. These are: pharmaceutical and zinc Bio-fortification of food gains.

Nutraceutical Interventions

Pharmaceutical Approach: Pharmaceutical approach has received most attention and involves the use of Zn-supplements to overcome health problems associated with Zn deficiency in humans. Results of a large number of such studies under the egis of International Zinc Nutrition Consultative Group (IZiNCG) are available in the two numbers of volume 25 of Food and Nutrition Bulletin (21, 11). Successful reduction in diarrhea in infants was reported by Bahal (15) and Bhatnagar (16) and of pneumonia by Bhandari (17). A meta-analysis of randomized controlled zinc supplemental trials reported an 18% decrease in diarrhea, a 25% decrease in diarrhea prevalence and a 41% fall in the incidence of pneumonia (26). Zinc supplements are reported to reduce the severity and duration of common cold (27, 28). Severe Zn deficiency has been reported to be associated with poor maternity outcomes (29). Maternal zinc supplementation improved fetal neurobehavioral development in Preu (18). In India, zinc supplements helped to reduce mortality among low-birth-weight infants (30). However, zinc content in breast milk has not been found to be correlated with maternal zinc intake (31, 32). Although not directly related, Zn-supplements are reported to lead to fewer episodes of malaria in Papua New Guinea (33).

Zinc supplementation is an assured and well controlled approach for zinc deficiency intervention in humans, but it has two problems:

1. Zinc supplements are to be used as per medical advice and thus its application is likely to be restricted to urban areas and millions of rural poor will not be able to adopt this approach.

2. It also involves additional expenditure and about one-third of the Indian population, which cannot afford even two square meals a day, cannot adopt this approach.

Zinc Enriched Foods: Zinc enriched foods have recently received considerable attention (34). Zinc enriched biscuits, idlis, vadas and other foods can be included in the school children's mid-day meal programmes already under-way in several states of India. This will involve only a little additional cost, but is implementable in urban as well as rural areas. Those involved with mid-day meal programmes must consult nutrition experts. However, production of zinc enriched foods call for the availability of zinc salts at grocery level rather than at a pharmacy as in the case of pharmaceutical approach. This will require development of zinc salt standards and provision of necessary regulation under Food Control Order to assure quality of such materials.

Diet Diversification: It is well known that animal foods (meat, poultry, eggs, fish, seafood's) and some vegetables and fruits are richer in zinc (Table 2) and their inclusion in diet can help in the intervention of zinc deficiency. Oysters are the richest source of zinc.

Bio-fortification of Food Grains

Genetic Bio-forification: Considering the wide-spread deficiencies of Vitamin A, iron and zinc, especially in the developing world, research on genetic bio-fortification of cereal grains and other foods with these micronutrients is going on in a big way under programmes, such as, HarvestPlus, Golden Rice and African Bio-fortified Sorghum Project (35). These projects involve GM (Genetic Modification) technology. Golden Rice has been engineered to express beta carotene by introducing a combination of genes that code for biosynthesis pathway for the production of pro-vitamin A in the endosperm (36). However there are problems in the acceptance of GM crops in several countries (37). So far no GM plant with denser zinc grains has been developed. In the cultivars so far studied, higher zinc concentration is generally associated with lower grain yield (38) and this is contrary to the goal of securing food security in a country. The major disadvantage of this approach is the huge amounts of funds and time required for developing GM crops.

Agronomic Bio-fortification: Agronomic biofortication of cereals (39) and pulses aims at increasing zinc concentration in grains through zinc fertilization. It has also been referred to as ferti-fortification (40). Zinc fertilizer applications are made on the basis of soil tests for available zinc in soil; the general recommendation for cereals and pulses is soil application of 5 kg Zn ha-1 as zinc sulphate hepta-hydrate (ZnSHH) at sowing (41). We have conducted a number of field experiments to compare different sources of zinc and methods of application. In studies on rice and oats ZnSHH was found to be superior to zinc oxide (ZnO) (Table 3). In rice, the Bio-fortification due to ZnSHH was 41.0% as compared to 35.6% with ZnO (42), while in oats the values were 34.1% and 30.0% for ZnSHH and ZnO (43), respectively. As regards method of application, foliar application was superior to soil application from the viewpoint of zinc fortification of grains. In corn, zinc fortification of grains was 14.4% with foliar application as compared to 10% with soil application (Table 4). Further, a combination of soil and foliar application recorded the highest increase of 21.4% in zinc concentration in corn grains (44). The ZnEDTA, a chelated zinc fertilizer was found superior to ZnSHH for soil application in rice (45) but not in chickpea (46) (Table 5). The amount of zinc applied as ZnEDTA was half that as ZnSHH. Three foliar sprays of ZnEDTA recorded the highest zinc fortification of grains in rice (42.9%) as well as in chickpea (69.7%). Even when soil application of zinc is made, a foliar application at grain filling stage of the crop is advantageous.

Varieties of a crop also differ in their response to zinc fertilization. For example in an experiment on chickpea, application of 7.5 kg Zn ha-1 increased zinc concentration in grain by 45.2% in variety 'Pusa 5028', while it was 33.1% in 'Pusa 2024' and 30.6% in 'Pusa 372' (47) (Table 6).

For all the experiments, data on grain yield are also provided to make the point that agronomic Bio-fortification of zinc in grains is made without any sacrifice on the yields. On the contrary zinc fertilization increases grain yield as well as zinc concentration in grain and is thus a win-win approach. Further even when GM crop cultivars with denser zinc grains are developed, they will need higher zinc applications.

Conclusion

Zinc deficiency in humans is an emerging problem in India and other Asian countries, where people mostly rely on cereals and pulses for their dietary needs. Agronomic Bio-fortification of cereals and pulses is the cheapest and fastest way to partly overcome this problem and this way zinc intake by humans can be increased without additional expenditure

Recommendation

Zinc agronomic Bio-fortification of cereals and pulses is the cheapest and fastest way to partly overcome this problem from the Indian populace and this way zinc intake by humans can be enhanced considerably.

Relevance of the study

The present review article is an eye opener to the health professionals, policy makers and planners to overcome the zinc deficiency problem from the Indian zinc deficient population in a shortest way.

Authors Contribution

Both the authors have equally contributed in the preparation of the manuscript

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Tables

TABLE 1 RECOMMENDED DIETARY ALLOWANCE (RDA) AND TOLERABLE UPPER INTAKE LEVELS (UIL) OF ZINC (MG DAY-1)

Age	RDA		UIL	
	Male	Female	Male	Female
0-6 month	2	2	4	4
7-12 month	3	3	5	5
1-3 years	3	3	7	7
4-8 years	5	5	12	12
9-13 years	8	8	23	23
14-18 years	11	9*	34	34
19+ years	11	8**	40	40

**Pregnant 12; lactating 13* ***Pregnant 11; lactating 12*
Adapted from: Institute of Medical, Food & Nutrition Board (2001)

TABLE 2 ZINC CONTENT IN SOME FOODS

Food item	mg Zn per serving	% Daily Value (DV)
Oysters, cooked, 3 ounces	74	493
Beef, chuck roast, 3 ounces	7	47
Crab, cooked, 3 ounces	6.5	43
Pork chop, Loin, cooked, 3 ounces	2.9	19
Chicken, cooked, 3 ounces	2.4	16

Chickpea, cooked, ½ cup	1.3	9
Rajma, cooked , ½ cup	0.9	6
Peas green, coked, ½ cup	0.5	3
Milk, low fat, 1 cup	1	7

DV is 15 mg for adults and children aged 4 years or older.
Adapted from National Institute of Health, Office of Dietary Supplement Zinc-Fact sheet for health Professionals (via internet)

TABLE 3 RELATIVE EFFICIENCY OF ZINC SULPHATEHEPTAHYDRATE (ZNSHH) AND ZINC OXIDE (ZNO) IN ZINC BIO-FORTIFICATIONOF RICE AND OATS

Source of Zn	Rice			Oats		
	Grain (tonnes ha-1)	Zn (mg kg-1)	% increase	Grain (tonnes ha-1)	Zn (mg kg-1)	% increase
Control	4.28	20.5	-	3.15	22.0	-
ZnSHH	4.68	28.9	41.0	3.79	29.5	34.1
ZnO	4.50	27.8	35.6	3.46	28.6	30.0
LSD (P=0.05)	0.21	NS	-	0.17	1.61	

NS=Not significant
Adapted from Shivay et al. (2013) & Shivay et al. (2014a)

TABLE 4 EFFECT OF METHOD OF ZINC APPLICATION ON GRAIN YIELD AND ZINC BIO-FORTIFICATION OF CORN GRAIN

Method of Zn application	Grain yield (tonnes ha-1)	Zn in grain (mg kg-1)	% increase in zinc over check
Control (no Zn)	4.4	40.2	-
Soil application , 5 kg Znha-1	4.7	44.2	10.0
Foliar application, 0.5% ZnSHH solution	4.42	46.0	14.4
Soil application , 5 kg Znha-1 + Foliar application, 0.5% ZnSHH solution	5.1	49.2	21.4
LSD (0.05)	0.38	2.0	-

Zinc applied as zinc sulphate heptahydrate (ZnSHH); A single foliar spray of 0.5 % ZnSHH supplied 0.5 kg Zn ha-1.
Adapted from Shivay and Prasad (2014)

TABLE 5 EFFECT OF SOURCES AND METHODS OF ZINC APPLICATION ON GRAIN YIELD AND ZINC CONCENTRATION IN RICE AND CHICKPEA GRAIN

Treatments	Rice			Chickpea		
	Grain yield (tonnes ha-1)	Zn in grain (mg kg-1)	% increase in zinc over check	Grain yield (tonnes ha-1)	Zn in grain (mg kg-1)	% increase in zinc over check
Control	4.78	21.2	-	1.84	42.6	-
Soil, ZnSHH	5.25	23.6	11.8	1.97	51.9	21.8
Soil, ZnEDTA	5.45	28.3	33.5	1.95	52.6	23.9
Foliar ZnSHH	5.56	28.7	35.4	2.14	58.4	37.1
Foliar ZnEDTA	5.88	30.3	42.9	2.25	72.3	69.7
LSD (P=0.05)		0.39	1.68	0.18	3.31	

Adapted from Shivay et al. (2014b, 2014c)

TABLE 6 EFFECTS OF ZINC LEVELS ON ZINC CONCENTRATION (MG KG-1 GRAIN) IN GRAIN OF THREE CHICKPEA VARIETIES

Treatments	Zinc concentration (mg kg-1) in chickpea grain at 2 levels	
Varieties	0 kg zinc ha-1	7.5 kg zinc ha-1
Pusa 2024 (Kabuli)	31.1	41.4
Pusa 5028	34.5	50.1
Pusa 372	35.3	46.1
LSD (P=0.05)	1.92	

Adapted from Shivay et al. (2014d)