Research Review

Sci Vis 9 (4), 159-165
October-December, 2009
ISSN 0975-6175

Hazard effects of excess of zinc in diet

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Received 13 December 2009 | Revised 24 December 2009 | Accepted 30 December 2009

ABSTRACT

Zinc (Zn) is one of the trace minerals which is required for huge range of bodily functions. Since last two decades, Zn as micronutrient is being used indiscriminately in agricultural and husbandry practices and also in baby foods and multivitamin supplements since Zn is non-toxic and promotes body weight in the consumers. Thus, the concentration of Zn in some vegetables and animals food products and other dietary food items has been increased. So far, the effects of long term Zn overload in the body have not been reviewed. Consumption of excess Zn in diet for longer period of time may contribute obesity and related diseases in adolescence, copper (Cu)-deficiency related abnormalities in the adults and pregnant women. Excess Zn in diet makes diabetic patients more vulnerable due to increase in glycosylated haemoglobin level in the blood. The various aspects about harmful effect of excess Zn in diet is given in this communication.

Key words: Diabetes mellitus; Cu; diet; obesity, pregnant women; Zn

INTRODUCTION

Several minerals serve as micronutrients and constitute important components of balanced diet. They are required in minute quantities for their participation in a number of life processes in the body. Zinc (Zn) is one of these several minerals and is required for a huge range of bodily functions. It is found virtually in every tissue of the body and is particularly important for the correct functioning of the immune system, for growth and development, and the anti-oxidant system and for the activity of a large number of Zn-dependent enzymes (approximately 300) both in plants and animals.

The main way in which it is used in the body is as an essential component (known as a "cofactor") for the functioning of a large number of enzymes, enabling the body to carry out the chemical reactions essential for life. Due to wide range of functions, daily requirements of Zn is 8 µg at 1 month of age decreasing to 5 µg at 4-12 months of age and subsequently it again increases to the order of 3-5 mg in 1-10 years old children. Normal adults on an average require 5-15 mg and pregnant women 10-25 mg Zn (Table 1).[1]

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Table 1. Recommended Dietary Allowance (RDA) of Zn for infants over 7 months, children, and adults (mg/day).

Age	Infants and children	Males	Females	Pregnancy	Lactation
7 months to 3 years	3	-	-	-	-
4 to 8 years	5	-	-	-	-
9 to 13 years	8	-	-	-	-
14 to 18 years	-	11	9	13	14
19 years +	-	11	8	11	12

Zinc-rich Foods

Zn is present in a wide variety of foods, particularly in association with foods rich in proteins. A vegetarian diet often contains less Zn than a meat-based diet. Rich sources of Zn for human consumption are nuts, wheat, legume, sea foods, dairy products, beans and lentils, yeasts, nuts and whole grain cereals and other animal products. Its quantity is very low in cereals, vegetables and fruits. White flour is a poor source, both because the Zn is mainly found in the outer layers of the grain, and because the fibre in grain contains phytates, which inhibit the absorption of minerals. Pumpkin seeds provide one of the most concentrated vegetarian food sources of Zn. Fortified foods including breakfast cereals make it easier to consume the recommended dietary allowance (RDA) for Zn (Table 1); however, they make it easier to consume too much Zn, especially if supplemental Zn is being taken.

Present Scenario about Zn

In spite of the impressive progress that has been made in the field of trace element nutrition in the past, the biological role and minimum requirement of trace elements are still hypothetical.[2] Since the minimum requirement of some of the trace elements is low, it is generally believed that a purely nutritional deficiency of these trace elements rarely occur in humans. The latest developments in the food technology enable the food industry to offer the general public in affluent countries an enormous choice of food products during the last couple of decades. Both deficiency of essential elements and toxicity of heavy elements are fairly common in many countries of Asia, Africa and Latin America.[3] In order to assess the nutritional importance of trace elements, it is relevant to consider the factors regulating their metabolism. Actual intake levels and bioavailability are two key factors that are nutritionally very important. Barring the occupational exposer, the food chain remains the major pathway through which trace elements enters human body. Only limited information is available from developing countries where trace element problems have low priority as dietary intake is often unsatisfactory since it is based on conventional techniques involving food tables.

During the last two decades, Zn as a micronutrient is being used indiscriminately in agricultural and animal husbandry practices and also in baby foods and multivitamin supplements with a view that Zn is non-toxic and promotes linear growth and body weight in the consumers. Percentage of Zn consumed from Zn-fortified food doubled from 14% (1994) to 28% (1998) in US pre-school children and for all age groups and the percentage of this will further increase over time.[4]

Recent survey on trace metal status of different vegetables in the state of Punjab around Chandigarh, India, revealed that due to use of different inputs in the fields by farmers during the growth of vegetables, Zn levels were recorded more than 40 and 120 mg of Zn/kg diet in above ground and underground vegetables (daily recommended range is 12.8-20 mg Zn/kg diet), but copper (Cu) was normal (Table 2).[5]

Even though Zn is an essential element in our diet, but too much can be harmful. Harmful effect of too much Zn generally begins at 10 to 15 time higher levels than the recommended dietary allowances of 5, 12, and 15 mg per day for infants, women and men, respectively.

Harmful Effects of Excess Zinc

Excessive presence of Zn in diet promotes absorption of nutrients and cell proliferation, acting through genes, resulting in the growth of individuals. The investigation conducted on growth hormone transgenic and genetically obese mice have shown that the growth promoting effect of Zn occurs through growth hormone whose activation is Zn dependent.[7] Excess of Zn intake during the growth phase increases the growth hormone level in the blood which enhances the growth rate, increases the number of fat cells in the body, promotes absorption of fat and elevates insulin activity. On withdrawal of growth hormone on approaching adulthood, the absorbed nutrients are directed to fat cells under the influence of elevated insulin activity where they are deposited as fat. The exogenous treatment of growth hormone or its analogues coupled with high concentration of Zn as $ZnSO_4$ in commercial feeds is being exploited in rearing livestock on large scale for higher yield of animal products. As a consequence of this, the animals grow faster and their tissues are loaded with fat and Zn. The unabsorbed Zn leaves the body along with the faeces that form the manure for agricultural used. Zn being equally essential for well being of plants, additional Zn in high amounts is employed as micronutrient in agriculture practices which results in elevation of its concentration in plants products also.

Table 2. Zn and Cu concentration in vegetables and other food stuffs found in the state of Punjab around Chandigarh and Manipur (where the level of Zn is higher while the Cu is within the normal range).[5,6]

Food stuffs	ZINC (Zn) mg/kg	COPPER (Cu) mg/kg
Wheat	46.2	46.8
Rice	40.8	58.8
Rajma	21.6	10.0
Bajra	38.4	31.8
Malka masher (pulse)	35.4	12.6
Horse pea	54.6	48.6
Mung	54.6	47.0
Kala chana	98.4	34.8
Peanut	34.8	48.0
Egg	109.8	46.8
Fish	78.0	51.0
Pork	174.0	48.0
Chicken	135.0	57.O

These food items loaded with Zn when consumed make the children grow faster and add some fat in their tissues which make them to appear healthy but impose serious health problems on attaining adulthood. The continuous input of excess nutrients in tissues particularly in fat cells caused by excess nutrients in tissues particularly in fat cells caused by Zn over a period of time contributes to obesity in adults. Obesity poses a formidable challenge to the growing population as it is etiologically linked to insulin resistance, an accompanying insulin dependent diabetes mellitus, hypertension and coronary artery disease.

Not only this, the excess free Zn ions in diet inhibited the Cu absorption as a consequence of the similar physiochemical properties of these two elements and Cu-Zn antagonistic reaction at intestinal level producing Cu-deficiency in them. The interaction between Zn and Cu is of practical concern because, it can occur with relatively low amount of Zn supplementation and Zn induced Cu-deficiencies are relatively easy to produced in adult humans.[8] Cu-deficiency further impairs enzymes of antioxidant system including superoxide dismutase, catalase and glutathione peroxidase and results in increasing the oxidative stress.[9] Cu-deficiency is also known to induce hypertension, increase blood cholesterol (hypercholesterolemia), and low density lipoprotein fraction increment in blood which lead to the condition favouring heart attack. The excess Zn ions on the other hand, either make the insulin inactive or binding of insulin with its receptor reduces due to Cu-deficiency and the existing risk factor of non-insulin dependent diabetes mellitus (NIDDM) are exacerbated.

Thus, intake of Zn-fortified food for longer periods of time may make the growing children more vulnerable to these diseases. Therefore, possible measures have to be taken to control the consumption of high Zn in diet and Zn-fortified foods.[4] An investigation reported that an increase of Zn in diet to double the amount of RDA increases the portion of the body fat in healthy children, and ultimately leads to obesity.[10]

A random survey of nutritionally adequate healthy young individuals (25-35 years) of Chandigarh population conducted by us showed a strong positive linear correlation of body mass index (BMI) and tissue Zn concentration. The overweight and obese people possessed higher Zn concentration in tissues than those of lean or normal body weight individuals. The descendants of NIDDM and ischemic heart disease patients (destined to develop NIDDM and ischemic diseases) possessed two to four time higher tissue Zn and less than half of Cu concentration than their counterparts of non-diabetic parents. This Cu and Zn imbalance continued for some time which after exceeding threshold level manifest as disease. Their perturbation caused by excess Zn in diet has links with obesity and obesity-related diseases among Indians. One of our studies on animal model revealed that the supplementation of Zn in amount equal to 80 mg/kg in semi-synthetic diet fed to the rats resulted in significant higher gain in their body weight, displayed significantly higher blood pressure and heart rates and their urine reacted positively with Benedict's test suggesting the onset of glucosuria in them.[11]

Mechanism of Zinc-induced Obesity

The mechanism behind the anabolic affects of excess Zn in diet is a result from higher absorption of nutrients, i.e., amino acids, fatty acid and glucose in addition to the activation of protein and nucleic acids syntheses. These anabolic effects of Zn are unlikely to diminish after cessation of growth. The continuous input of excess nutrients in tissues by excessive bioavailability of Zn after adolescence may create environment essential for obesity. Excessive Zn in diet promotes deposition of fat and increase in adiposity and the number of adipocytes leading to obesity.

The potential mechanism for development of

obesity involving Zn is due to the activation of ovine metallothioneine ovine growth hormone transgene (OMT-la-OGH) by $ZnSO_4$ as it activates the genes of growth hormone during early period of growth and induces the relatively undifferentiated preadipocytes to be committed to become adipocytes.[12] This may increase their population. The enhanced population of adipocytes responds by filling with triacylglycerol due to increased absorption of nutrients caused by Zn and eventually leads to the observed state of obesity. In our previous study, it was shown that obese of both the sexes possess higher Zn concentration in their hair than those with normal body weight for their height and BMI.[13]

High Zinc Diet and Diabetic Patients

Consumption of excess of Zn in the diet also makes diabetic patients more vulnerable to harmful effects. When excess Zn is taken for a longer period of time by diabetic patients, it increases in the level of glycosylated haemoglobin (HbA_{1c}), urinary Zn excretions and altered glycosylation.[9] High level of HbA_{1c} is a reliable quantitative indicator of long-term increase of blood sugar level (hyperglycaemia) and it also contributes to the changes in the profile of blood trace elements, and as results of these, the degree of oxidative stress increases further.[14] During high Zn-supplementation in individuals with diabetes results in high serum Zn concentrations and block insulin receptors of cell and leads to decreased glucose tolerance.

Moreover, the use of Zn supplements in free-living population has been discouraged because it results in Cu deficiency. Some other potential toxic effect of Zn supplementation in patients with diabetes mellitus is that high doses of Zn in normal adults increased the low density lipoprotein (LDL) and decreased in high density lipoprotein (HDL) cholesterol. This leads to a condition to the patients favouring the increase severity of hypertension, coronary heart diseases and diabetes mellitus etc.[15]

High Zinc Diet and Pregnant Women

When there is presence of excess Zn in the diet of pregnant women, it can induce fetal Cu-deficiency and negatively affect human pregnancy. This condition is also found in experimental animals where maternal Zn supplementation can induce fetal Cu-deficiency.[16] Long term deficiency of Cu in pregnant women and animals results in early embryonic death, gross structural anomalies including skeletal, pulmonary and cardiovascular defects and persistent biological, neurological and immunological abnormalities.[17] It leads to the acute respiratory distress syndrome in neonatal rats and premature infants. The respiratory distress syndrome may be the major cause of the morbidity among the premature infants.[18] So, it is reasonably to argue the caution to be taken when pregnant women are given Zn supplementation. Consistent with this the Institute of Medicine, Washington DC, USA, has recommended that the Cu supplement should provide with Zn supplements are given during pregnancy.[19]

A study in Nepal also reported that high amount of Zn given during gestation periods blocks the beneficial effects of iron/folate and reduced the amount of hemoglobin levels resulting in malformation in the neonate.[20] In our laboratory, an investigation was carried out by supplementing the Zn in amount equal to 80 mg/kg in fat and refined sugar based semi-synthetic diet fed to the pregnant rats produced neonates which had lower body weight with various malformations such as uncoordinated movement of body part, smaller eye size and the higher ratio of 'head' to 'rest of the body'. None of them could complete the weaning period and died at different time intervals.[21]

Conclusion

The obesity and its related diseases like hypertension, diabetes mellitus, heart diseases and neonatal defects though are genetic disorders but their dramatic rise and their onset at rela-

tively young age Indian population during the last two decades is rather a recent phenomenon associated with agriculture boom achieved through excessive and extensive used of micronutrients in which Zn stands prominently. The abandoning of traditional Cu containing metallic utensils, the compulsory sources of Cu through its leaching into food during cooking has further aggravated the condition. Zn management in food therefore is essential to contain the obesity related diseases. This can be targeted by immediate and long term strategies.

The immediate strategy involves the restricted consumption of Zn rich food items such as cheese, meat, eggs, nuts, and wheat products, and increased inclusion of Zn binding products such as fibre leafy vegetables and phytate rich legumes such as soyabean and its product that should reduce its bioavailability. This is particularly important for those who have genetic predisposition, i.e., family history of these disorders, irrespective of signs of clinical symptoms. The use of Cu utensils for cooking will not only help in preventing the Cu deficiency but also reduced the influx of Zn in them. The long term strategies require a stator controlled used of Zn in commercial feeds and agriculture practices through legislation in interest of human health, otherwise the obesity-related diseases would dominate further in the days to come.

ACKNOWLEDGEMENT

Thanks are due to University Grant Commission, North Eastern Regional Office (UGC-NERO) for providing financial assistance to K. Birla Singh, under Minor Research Project. Financial aid provided by University Grants Commission, New Delhi under Centre for Advance Study, to the Zoology Department, Panjab University, Chandigarh is gratefully acknowledged.

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