THE ROLE OF ZINC IN IMPROVEMENT OF WEIGHT GAIN OF CHILDREN WITH PROTEIN ENERGY MALNUTRITION

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Abstract:

Background:

In many developing countries micronutrient deficiencies-including zinc- are prevalent in children. To provide stronger bases for addressing the importance of zinc in growth promotion and weight gain, this systematic literature review was conducted.

Data sources:

Studies published in English language were retrieved by searching MEDLINE (1966-2005) as well as manual searching for journals with relevant articles.

Study selection:

Only randomized controlled trials with results adjusted for children age, socioeconomic status and nutritional status (according to Z-scores) were included. As well as information on study design, sample size and outcome measures.

Results:

Seven studies met the inclusion criteria for the systematic review with regard to the effect of zinc on promotion of weight gain in

malnourished children. Five studies showed a significant weight gain after supplementation with zinc, while two studies showed no effect.

Conclusion:

It was concluded that zinc has a positive effect on weight gain promotion in malnourished children. However, more researches are needed to understand the mechanism of zinc on different body systems and functions, its effect on child health and whether, its positive effect holds for its intervention as part of nutritional programmes.

Introduction:

Malnutrition is frequently part of a vicious cycle that includes poverty and disease. These three factors are interlinked in such a way that each contributes to the presence and permanence of the others. Socioeconomic and political changes that improve health and nutrition can break the cycle; as can specific nutrition and health interventions (1).
Malnutrition usually refers to a number of diseases, each with a specific cause related to one or more nutrients, for example protein, iodine, vitamin A or iron. In the present context malnutrition is synonymous with protein-energy malnutrition, which signifies an imbalance between the supply of protein and energy and the body's demand for them to ensure optimal growth and function. This imbalance includes both inadequate and excessive energy intake; the former leading to malnutrition in the form of wasting, stunting and underweight, and the latter resulting in overweight

and obesity (1). Trace mineral deficiencies underlying protein-energy malnutrition (PEM) are being increasingly recognized. These may occur concomitantly with PEM or become overt during the recovery phase. Iron (Fe), zinc (Zn), and copper (Cu)

Malnutrition are associated with PEM (2). Increased gastrointestinal losses coupled to greater need for rapid growth are considered important causative factors.

Zinc is an essential nutrient, which is required to maintain the normal structure and functions of multiple enzymes, including those that are involved in transcription and translation of genetic materials and therefore in cell division (3). Zinc has a fundamental role in many aspects of cellular metabolism (4), is critical for normal immune function (5) and physical growth (6). Zinc deficiency appears to be widespread in low-income countries because of a low dietary intake of Zinc-rich animal source foods and a high consumption of cereal grains and legumes, which contain inhibitors of Zinc absorption (7,8). Children in poor countries are also frequently affected by diarrhea, which causes excess fecal losses of Zinc (9). In such settings, Zinc supplementation has been shown to reduce the rates of diarrhea and pneumonia (10) and to enhance the physical growth of young children at risk of stunting (6).

Zinc might also influence the growth of young children particularly in resource poor countries where dietary intake or absorption of Zinc may be inadequate (11) and excessive Zinc loses may occur due to frequent enteric infections (12). Nevertheless, the lack of simple objective biomarkers of Zinc status has hindered the ability to implicate Zinc nutriture unequivocally as a cause of growth failure in human.

During the last two decades, Zinc deficit has been identified in human with inadequate intake or with various dietary factors that interfere with Zinc absorption. Fiber, phytates, and other minerals such as Cu have been demonstrated to decrease Zinc bioavailability (13). Zinc nutritional status is highly dependant on absorption from diet since body stores of these essential elements are quite small (14). Zinc needs for optimal growth have not been fully defined for either normal or malnourished children. Nevertheless, studies in animals and human suggest that Zinc requirements are increased during rapid growth. There are reasons to suspect that malnourished children may be Zinc deficient, including their frequent consumption of diets that have inadequate Zinc contents (15), and a high prevalence of diarrhea (16). Golden et al have demonstrated in malnourished infants that inadequate Zinc intake may be a limiting factor for growth (17).

Objective:

To review the available data on the effect of zinc on the improvement of weight gain in children under five years of age with protein energy malnutrition.

Methods:

Identification of studies:

- A search was conducted in MEDLINE (1966-Feb 2005).
- Manual search for journals with relevant articles.

Inclusion criteria:

- Randomized double blinded placebo controlled trials.
- Restricted to studies of malnourished subjects, as evidenced by

mean initial anthropometric Z-scores (<-2.0Z).

- Subjects age below 5 years of age.

Exclusion criteria:

- Studies were excluded if there were reports, editorials, or letters to the editor.
- If they did not provide complete data.
- If the subjects were suffering from severe infection or chronic illness.

Results of the studies:

Table (1) shows the results of the seven reviewed trials which measure weight gain in response to zinc supplementation. Four trials were conducted in Asia, Bangladesh (2 trials), Pakistan, and Vietnam. The other three trials were conducted in different countries, Chile, Israel, and Ethiopia. The trials were different in terms of sample size, age of the patients, duration of Zn supplementation, Zn dose, and primary outcome result.

Khantun: 20 mg/day in two divided doses, Roy Sk: 20 mg/day in three divided doses, Bhutta: 3 mg/kg/day as single dose, Castillo: 2 mg/kg/day as single dose, Hershkovitz: 2mg/kg/day as single dose, Ninh: 10 mg/day as single dose, and Umeta: 10 mg/day as single dose.

- Five studies found a significantly increased weight gain in Zn supplemented subjects compared with the control.
- Two studies concluded that there was no effect of Zn supplementation on weight gain.

Table (1): Results of the studies:

Study	Study duration	Sample size	Age of the subjects	Intervention	Primary outcome: *weight gain*	Secondary outcome
Khantun et al, 2001 Bangladesh (18)	One week	**48** (Zn n=24) (C. n=24)	6-24 months	-Subj received dietary supp. (not stated), -Zn grp received 20 mg/d in multivits bd, -ctrl received multivits	**P<0.045**	-Stool freq (n/day) -Stool wt (mg/kg/body wt)
Roy Sk et al, 1997 Bangladesh (19)	Eight weeks	**111**(Zn n=57) (C. n=54)	3-24 months	-Subj received dietary supp. (670kcal/d, prot. 17g/d) -Zn grp received 20 mg/d in multivits tds, -ctrl received multivits	**P<0.03**	Stool output
Bhutta Za et al, 1999 Pakistan (20)	Two weeks	**87** (Zn n=43) (C. n=44)	6-36 months	-Subj received dietary supp. (100kcal/kg/d) -Zn grp received 3 mg/kg/d once in multivits -ctrl received multivits	**Not sig.**	-Stool freq (n/day) -IGF-1 level
Castillo et al, 1987 Chile (21)	Two months	**32** (Zn n=16) (C. n=16)	2-12 months	-Subj received dietary supp. (150kcal/kg/d, 5g/kg/d) -Zn grp received 2 mg/kg/d once in multivits -ctrl received multivits	**P<0.05**	Diarrhea episode, RTI, pyoderma

Herchkovitz E et al, 1999 Israel (22)	Three months	**25** (Zn n=14) (C. n=11)	3-9 months	-Subj received dietary supp. (127kcal/d) -Zn grp received 2 mg/kg/d once in multivits -ctrl received multivits	**Not sig.**	IGF-1 level
Ninh Nx et al, 1996 Vietnam (23)	Five months	**146** (Zn n=73) (C. n=73)	4-36 months	-Subj received dietary supp. (not stated), -Zn grp received 10 mg/d once in multivits -ctrl received multivits	**P<0.001**	-IGF-1 level -Diarrhea episode, RTI
Umeta M. et al, 2000 Ethiopia (24)	Six months	**100** (Zn n=50) (C. n=50)	6-12 months	-Subj received dietary supp. (not stated), -Zn grp received 10 mg/d in multivits -ctrl received multivits	**P<0.001**	Diarrhea episode, RTI

Discussion:

The strengths of these studies included their randomized, double-blind design and the supervised administration of the supplements. The differences in children sex, ages, dietary formulas being offered to patients, duration and amount of zinc supplementation will be controlled when a meta-analysis is conducted for these studies.

The mechanism by which Zinc supplementation might promote weight gain in malnourished children is unknown. This effect may result from increased apetite and improved ingestion of energy and protein. Nevertheless, increased apetite is not a consistent clinical finding of Zinc supplementation (25).

Zinc supplementation rapidly improves intestinal transport systems, cellular sodium homeostasis and mucosal integrity. Therefore, adding Zinc to oral rehydration salt might improve both immediate and long term recovery from diarrhea (26). Golden et al noted improved efficiency of energy utilization after Zinc supplementation but did not report infectious morbidity before and after Zinc (17).

Zinc supplementation was not effective in two studies. Possible explanation could be the specific characteristics of the study population that may have affected their ability to respond to Zinc. In the study of Bhutta et al it is likely that the study represented a more severe spectrum of diarrhea, i. e. the rate of Zn absorption is affected by the rate of enteric infection (20). Moreover the nature of the local diet can affect Zinc status if it contains more phytates which could lead to insufficient absorption (27). The sample size in Herchkovitz study may have been too small to detect an effect on weight with statistical confidence(22).

It is as well possible that administering Zinc at an early stage of rehabilitation has a direct detrimental effect on the immune system during an infection and it is better to be administered at a later stage of rehabilitation when it is much less likely that sepsis is ongoing (28). The discrepancy between the absence of weight gain and the significant increase in circulating IGF-1 levels (by more than 60%) is puzzling (22). It is possible that micronutrients deficiency could inhibit the growth promoting properties of the increased blood concentration of IGF-1 level (29).

Again limitations were experienced to be certain whether subjects studied have indeed consumed the recommended amounts since eating problems are not uncommon in this group (30)

Inter-subject heterogeneity of the outcome:

In evaluating the effect of Zinc on weight gain, it is important to emphasize the heterogeneous nature of the outcome. Not all malnourished children who had been supplemented with Zinc showed increased weight gain. Some patients showed increased weight gain in the first week while others showed it after 2-3 weeks.

Implications for future research:

It is still not clear why weight responses to supplemental Zinc are inconsistent in different studies. Studies have consistently demonstrated a reduced incidence and severity of infections, like diarrhea and acute lower respiratory tract infections following Zinc supplementation, leading to reduced morbidity and mortality among high risk children (31, 32, 33). Studies are needed to look into the different mechanisms of Zinc action on growth promotion. As well there is a need for prior screening of zinc status, differential dosing or both. Nevertheless even if growth is not

affected by supplemental Zinc, there are other important reasons to consider intervention to enhance Zinc status in malnourished children eg. reduced infectious morbidity. In poor settings Zinc supplementation has been shown to reduce the rates of diarrhea and pneumonia (10) and to enhance the physical growth of children at risk of stunting (6). Thus more studies are needed in a range of different populations to establish appropriate policy recommendations concerning the optimal use of Zinc supplements whether alone or in combination with other multiple micronutrients.

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