

## Effect of zinc supplementation on appetite, growth & body composition in children suffering from non-specific etiology of feeding refusal with failure to thrive

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### Abstract

In order to evaluate effect of zinc supplementation on appetite, growth and body composition in children suffering from non specific etiology of poor feeding associated with failure to thrive (FTT), we conducted a double blind randomized control trial (RCT). Children between 36 to 72 months having weight for age between 60% to 89% of National Center for Health Statistics (NCHS) median and not gaining weight satisfactorily (weight gain less than 100gm in last 3 months) but developmentally normal and active child with no apparent significant acute or chronic medical or surgical disorders during last 3 months were included in the study. We initially assessed 100 such children. After fulfilling inclusion criteria, finally 40 children were allocated in RCT to receive supplementation with either oral zinc 20 mg/day mixed with multivitamin (Group A, n=20) or oral multivitamin only (Group B, n=20) for 21 days. Both the groups were comparable with respect to initial baseline characteristics including anthropometric, body composition and zinc status. Body composition was measured by using bioelectric Impedence analysis (BIA). Children assessed one month after initiation of intervention revealed significant number of

children in group A developed improved appetite in comparison to group B (60% VS 15%, RR 8, 95% CI 1.75-36.48). Increase appetite was associated with significant increase in weight gain, in group A in comparison to group B (RR 9, 95% CI 1.64-49.41). Increase weight gain was associate with increased fat free body mass (FFBM) in majority of children in group A. No significant side effect were report in each group. However 50% children in group A, whose appetite increased with zinc supplement, developed reappearance of their poor appetite after completion of zinc supplement. It can be concluded from the study that oral zinc supplement can help in improving appetite associated with weight gain in children with poor feeding due to non-specific cause with FTT without any adverse effect on body composition.

### Key words

Zinc, appetite, weight gain, body composition, children, Bangladesh.

### Introduction

Zinc is a very essential micronutrient and has important role in child health and development. Zinc which is present in more than 100 metalloenzymes, has been among the essential micronutrients necessary for growth and prevention of infections. Zinc is essential for protein synthesis, including immunoglobulin and mediators of cell mediated immunity.<sup>1</sup> Zinc deficient children are vulnerable to infectious disease including pneumonia, even in anthropometrically well nourished children.<sup>2</sup> Children receiving supplemental zinc recovered earlier from acute and persistent diarrhoea than the control children.<sup>3,4</sup> several studies have documented the effect of zinc supplementation on growth.<sup>5</sup> One interesting property of zinc is that it improves test equity.<sup>6</sup> One of the most

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frequent paediatric problem, mostly among children of middle and higher socioeconomic class which concern parents and for which frequent paediatric consultations are sought both at hospital paediatric outpatient level and paediatric private surgery is feeding refusal with or without failure to thrive in otherwise developmentally normal, non sick and physically active children. Both parents and paediatricians not infrequently become frustrated as most of the times little can be done, to improve child's eating behaviour. Zinc supplementations to such children are now practiced in Bangladesh by some health care providers on the basis of unpublished observation that it may improve appetite and weight gain to such children. However, there are concerns also among health care providers which include paediatrician in particular, whether zinc supplementation to such children adversely affects the child including adverse effect on body composition. However objective evidence of the effects of zinc supplementation on human appetite is woefully limited and to date no such published controlled study done in Indian subcontinent. We therefore undertook the study to test our hypothesis that zinc supplementation improve the appetite associated with weight gain in children suffering from nonspecific etiology of feeding refusal with failure to thrive without any significant harmful effect including adverse effect on body composition.

### Subjects and methods

During a 12 months period, a double blind randomized controlled interventional study involving children between 36 months to 72 months with primary complaints by parents of poor appetite and not gaining weight more than 100 gm during last three months follow up but without any clinical evidence of significant acute or chronic medical or surgical problems currently or during last three months with developmentally normal and active children were included in the study. Severely undernourished and anthropometrically normal or over weight children were excluded from the study and weight for age between 60%-89% of NCHS were included in the study.

In all provisionally selected children blood was drawn for complete blood count and blood film study and urine were collected for routine test and culture. Routine investigation for stool was also done for ova, protozoa and cyst, for possible parasitic infestation. Children having haemoglobin more than 10 gm/dl with normochromic normocytic blood picture and no significant bacteriuria in urine culture, with no protozoa cyst and ova on routine stool examination were included in the study. Weight was measured by digital (Seca model 835, Todd scales UK) weight machine with graduation to 20 gm. Body composition was measured using BIA, which is reliable, valid, safe, noninvasive approach for rapid measurements human body composition.<sup>7</sup> It was performed in all two groups of children, before intervention and after the end of one month of study of children of zinc intervention group only whose weight increased significantly with improved appetite by portable bioelectric impedance analyzer (Body stat model 1500, Body stat Limited, Isle of Man, British Isles) using tetra polar electrode, placing two electrode in right lower limbs and two in upper right limbs. An electric impulse of 800 MA at 50 KHZ was then passed through the body of the child and reading of the resistant (electric impedance) was recorded<sup>7</sup>. A linear regression equation was used to calculate the total body water (TBW), FFBM or lean mass using age specific formulas and age specific constants of body density.<sup>8,9</sup> Fat mass (FM), percentage of fat mass and percentage of body solid were then calculated simply from percentage of FFBM and percentage of TBW respectively. Zinc was estimated by flame atomic absorption spectrophotometry. Serum and hair zinc was considered low if it was <100 microgram/dl and <150 microgram/gm respectively. Children were excluded from the study showing genuine intolerance to drugs which includes vomiting and noncompliance to take drugs for specified period. Children taking zinc supplement during last three months were also excluded from the study. Children's mothers were supplied with questionnaires, which included feeding behavior and possible side effects they have observed during supplementation of the drugs.

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Children were enrolled in the study after taking informed consent from their mother.



Figure 1: Portable bioelectric impedance analyzer(BIA)

Eligible children were allotted to double blind randomized controlled trial to receive either oral zinc (Zn) supplement (20 mg/day, Group A) mixed with multivitamin syrup (Zn + MV) or multivitamin (MV) syrup (Group B) alone for 21 days. Simple randomization techniques were done using a computer programme. Medicines were supplied in bottles that were similar in size, shape and colours without any commercial label. Neither the patient nor the attending physician, appointed to the study knew which of the two drugs the patient received. The bottles were coded and only the principal investigator who was not directly involved in delivering drugs to patients knew which bottle contain which drug. Patients were followed up on 14th day, 21st day and at the end of one month of the study.

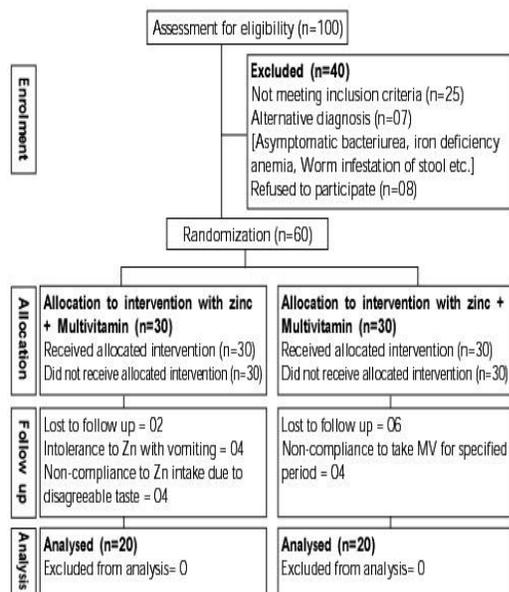


Figure 2 : Flow sheet chart

Patients appetite, adverse effects associated with drug intake and weight were assessed in each occasion. Body composition, serum & hair zinc status were assessed in all, finally analyzed children of both group A & B before intervention and at the end of one month of the study only to those children whose appetite improved associated with significant weight gain in group A only. Weight gain was considered significant if weight gain increased by more than 5% of body weight one month after the study. Strength of association (affect size) of improved appetite and weight gain associated with zinc supplement and precision of affect size were assessed by measuring risk ratio (RR) and 95% confidence interval (CI) of RR respectively. A RR was considered significant if 95% CI of RR did not include 1, excluding null hypothesis.

## Results

Of 100 children assessed for eating disorder associated with failure to thrive, 40 children (Zn + MV=20, MV=20) completed the study (Fig 2). Baseline characteristics, anthropometric, BMI, body composition and serum and hair zinc in two groups were comparable (Table- 1, 2, 3, 4 & 5).

Table-1 : Sex distribution

Sex	Group- A (Zinc + MV)	Group-B (only MV)
Male	14	12
Female	6	8

Table-2 : Age distribution in months

Age	Group- A (n 20)	Group-B (n 20)
36-47	7	8
48-59	8	5
60-72	5	7

Table-3 : Anthropometric measurement

	Group- A	Group-B
Weight for age*	75.30 ± 6.25	78.50 ± 8.52

Height for age	90.47 ± 4.28	91.35 ± 3.78
Weight for height	85.42 ± 3.89	86.35 ± 3.48
Body mass index (BMI Wt kg/h <sup>2</sup> in meter)	14.6 ± 1.70	14.8 ± 1.85 U

\*% NCHS median

Table-4 : Initial zinc status

Group	Serum zinc (micro gm/dl)	Hair zinc (micro gm/gm)
A	141 ± 54.70	184 ± 48.60
B	152 ± 39.24	192 ± 82.54

Table-5 : Body composition &amp; BMI

Group	% TBW	% FFBW	% FM	% Body solid	BMI	Impedance
A	60.83 ± 3.56	76.89 ± 8.29	23.10 ± 8.31	39.17 ± 3.38	14.06 ± 1.70	802 ± 141
B	62.22 ± 4.56	77.32 ± 7.31	22.68 ± 7.68	37.78 ± 4.42	15.8 ± 1.85	779 ± 132

Table-6 : Improved appetite evaluated after one month

Group	Yes	No
A	12(60%)	8(40%)
B	3(15%)	18(90%)

RR 9,95% Ci 1.752, 36.48

Table-7 : Weight gain (&gt;5% weight gain) after one month

Group	Yes	No
A	10(50%)	10(50%)
B	2(10%)	18(90%)

RR 9,95% Ci 1.638, 49.41

According to mother's assessment in group A, improved appetite at the end of one month were found in group A (Zn+MV) in 12 (60%) children, of them 10 (50%) children achieved significant weight gain, in comparison to 3 children (15%) showing increased appetite of them 2(10%) children showing significant weight gain in group B (MV alone). This improvement of appetite and weight gain in children of group A were found statistically significantly in comparison to children of group B (Table 6 & 7).

Table-8: Effect on body composition before &amp; after zinc supplement of 10 children whose weight increased significantly associated with improved appetite with zinc supplement

Sl	Age (Month)	Sex	Weight (Kg)	BMI	TBW	%FFBS	%FAT	%IMP
1	50	M	14.50 15.20	15.4 16.2	60.30 63.72	79.40 83.16	20.60 16.84	967 695
2	61	M	15.00 16.50	13.9 15.3	59.62 63.71	76.83 82.10	23.17 17.90	869 733
3	48	M	14.50 16.00	13.4 14.8	55.38 56.2	71.37 72.40	28.62 27.60	974 862
4	46	M	12.50 13.50	13.6 14.7	61.4 65.28	79.00 84.14	21.00 15.86	871 752
5	57	M	12.80 14.10	14.2 15.1	58.41 59.20	73.80 76.00	26.20 24.00	892 780
6	68	M	18.00 19.20	14.4 15.1	54.19 59.45	68.8 75.49	31.2 24.51	940 780
7	55	M	14.50 15.80	15.4 16.2	60.83 53.78	79.04 70.20	20.60 29.80	<b>767</b> <b>798</b>
8	64	M	14.00 14.90	12.9 14.2	64.30 58.40	82.87 75.38	17.12 24.6	<b>863</b> <b>893</b>
9	66	M	15.20 16.00	14.3 15.1	58.92 62.32	76.92 81.36	23.10 18.63	851 760
10	41	M	12.80 14.00	14.2 15.00	57.50 59.62	73.81 76.53	26.19 23.47	892 780

Body composition of 10 children whose weight (Table-8) increased significantly by zinc supplement showed 8 (80%) children's weight gain were associated with increase of FFBM without increase in body fat. Serum zinc increased from initial 131±28.70 mg/dl to 184±45.20 mg/dl after zinc intervention while hair zinc before & after intervention was 178±42.24 mg/gm & 182±472.56 mg/gm in 10 children whose appetite increase with weight gain in zinc intervention group. No significant side effects were reported or observed of 12 children whose appetite increased. However, 6 out of 12 children mother, who showed improved appetite with zinc supplement for 21 days, reported reappearance of poor appetite of their children, when zinc supplement discontinued after 21 days.

## Discussion

This pilot study revealed that zinc supplements improves appetite associated with weight gain significantly in children with non-specific aetiology of feeding refusal with failure to thrive, when compared with control children taking multivitamin only. Our study also found that increase appetite associated with weight gain do not adversely affect the body composition as evidenced by desirable

increase in FFBM or lean body tissue without increase in undesirable increase in fat mass, in majority (80%) of children with weight gain. No significant side effects were observed during 21 days ingestion of zinc supplement. However mother of half of their children whose appetite improved, reported that eating disorder reappeared, when zinc supplement was discontinued after 21 days and weight gain was in their opinion was possibly due to increased appetite during the 21 days supplement of zinc. Beneficial effect of zinc in children in childhood diarrhoea is well-established and routinely used in Bangladesh as recommended by WHO. However zinc supplement is also occasionally used by some medical practitioners in Bangladesh with unpublished observation that it improves poor appetite in children which is frequently the primary complaint by parents for which medical consultations are sought in private medical practice in particular. We realize that the relationship of improved appetite associated with weight gain by zinc supplementation remains controversial and its use in such condition is a matter of concern to some medical practitioners. Objective evidence of the effect of zinc supplementation on human appetite is however limited at this time. A milder form of zinc deficiency with slight growth retardation, poor appetite with impaired taste acuity was discovered in children of middle and upper income family, in Denever, Colorado, USA who were presumed to be in good nutritional status, whose taste acuity and anorexia hypogausia and pica improved with zinc supplement<sup>10</sup>. Krebs MF et al also observed increased food intake of young children receiving zinc supplement.<sup>11</sup> Anorexia, pica and poor growth in Chinese preschool children were associated with zinc deficiency in Beijing, China, which were corrected by zinc supplement<sup>12</sup>. Although unpublished observations by many health service providers in Bangladesh have demonstrated an increase appetite associated with weight gain with zinc supplement in children suffering from anorexia there is no published study in such condition. The study is unique in the sense that very few published studies done elsewhere on effect of zinc supplement on anorexia in human body were

not placebo or cases controlled and were not double or single blinded and no study demonstrated the effect of zinc on body composition in such conditions. An interesting finding of our study was that our study cases were not initially biochemically hypozincaemic, although weight gain and improvement of anorexia by zinc supplementation were associated with increase in serum zinc level. This is in disagreement with studies done elsewhere where anorexia were associated with low serum zinc level (serum zinc <100 mg/dl), which improved with zinc supplementation<sup>10,12</sup>. This finding can be explained by the fact, that since there is no single assay of zinc that can confidently and comprehensively assess zinc status of human body and there is no single reference range of normal serum zinc level, it is now widely recognized that the best way to demonstrate zinc deficiency is to observe clinical response with specific conditions with appropriate control.<sup>13,14</sup> Change in eating behaviour found in our study with zinc supplement is useful in this regard just as growth response is observed with zinc supplement<sup>13</sup>. The beneficial effect of zinc supplement may be due to correction of latent zinc deficiency or direct stimulant effect of zinc on taste acuity or both, which may be analogous to immunostimulant effect of zinc supplement independent of zinc depletion<sup>1,15</sup>. Golden MHN et al found weight gain of zinc supplemented children associated with formation of lean tissue instead of adipose tissue<sup>16</sup>. This was consistent with our study where we found majority of our children weight gain was associated with increase in FFMS instead of fat mass. Two children weight gain associated with fat mass could be due to direct effect of increased appetite without any influence of zinc on body composition.

Zinc has physiological role in normal taste sensation and improves taste acuity<sup>10</sup>. Moreover many cases of zinc deficient and idiopathic hypogeusia have been corrected by zinc supplementation in adults<sup>17</sup>. Our study however revealed that 50% of children whose eating disorder improved with zinc

supplement stopped feeding well when zinc supplement discontinues, which indicates short term benefit and high relapse rate of eating disorder in 50% children who responded well with Zn supplement for 21 days. This can be explained by the fact, that beneficial effect of zinc can be observed best in the presence of pre-existing low serum zinc level<sup>18, 19</sup>. Our study populations were not biochemically hypo-zincaemic initially. Pre-treatment hypo-zincaemic status if found in our study could have more durable and beneficial effect on eating disorders. Instead of 21 days of zinc supplement, more prolonged course (3 to 6 months) of zinc supplement or zinc fortified food, may have long lasting effect as found by Chinese study<sup>12</sup>. No significant side effects were reported during 21 days zinc supplement of children who were finally analyzed. However 4 children showed intolerance to zinc supplement with vomiting, who were excluded from final analysis. Our study has the weakness in the fact that sample size of study population was small. The result of our study once confirmed by the ongoing adequately powered placebo controlled multicentre studies, will raise the important question whether public health measures should be taken to improve appetite and growth in growth retarded eating disorder children, in the absence of acute or chronic medical or surgical illness.

### Conclusion

From the study result we conclude, that zinc supplementation improves appetite and weight in significant number of children with poor appetite and growth failure due to nonspecific cause, even though they are biochemically not hypo-zincaemic without any adverse effect including adverse effect on body composition, which is consistent with our hypothesis that zinc supplement improves poor appetite associated with failure to thrive. However this beneficial effect was brief in half of the children, whose eating disorder reappeared when zinc supplement was discontinued. It is worth while giving a trial of zinc supplementation in children with eating disorders in the absence of any other nutritional deficiency or illness. However it

was a pilot study and therefore further adequately powered multicentered randomized control trials are needed in order to validate our findings.

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