Effect of Zinc Supplementation on Linear Growth and Bone Mineral Density in Prepubertal Children with β -Thalassemia Major

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Abstract

Background:Linear growth and bone mineral density are commonly affected in thalassemic children and the aetiology is usually multifactorial.

Objective: To study the effect of zinc supplementation on linear growth and bone mineral density in prepubertal children with beta- thalassemia major.

Methodology:This is an intervention study at hematology clinic,Ain –Shams university,started at Aptil 2012. until April 2014. Forty prepubertal osteoporotic thalassemic children Ninteen males and twenty one females ,were supplemented with oral zinc sulfate capsule,once daily for 12 months consecutively . Height percentile (plotted on DEMPU curves), serum zinc level and BMD Z- score (measured by DEXA) were measured both before and after zinc intake.

Results:There was statistically significant improvement when height percentile,serum zinc level andBMD Z-score were measured before and after zinc supplementation (P value < 0.001). There was no statistically significant difference between males and females when all these parameters were measured either before or after zinc supplementation (P value > 0.05).

Conclusion: Zinc supplementation had a positive impact on linear growth and BMD in prepubertal children with beta- thalassemia major and this effect couldhave been magnified if zinc was provided at an earlier age and for a longer time.

Key words: zinc supplementation –linear growth –prepubertal children –beta thalassemia major

أثر أعطاء الزنك على الكثافة المعدنية للعظام والنمو الخطى فى سن ما قبل البلوغ للاطفال المصابين انيميه البحر المتوسط

تعد مشكلة نقص النمو الطولي و نقص كثافة أملاح العظام وما يتبعه من حدوث هشاشة بالعظام من المشكلات الشائعة في الاطفال اللذين يعانون من انيميا البحر المتوسط، خاصة قبل سن البلوغ، وهذا بدوره يؤدي الى ضعف العظام و زيادة قابليتها للكسور مما قد يتعارض مع الامشطة اليومية لهؤلاء الاطفال.

و تهدف هذه الدراسة الى تقييم نتائج اعطاء عنصر الزنك لهؤلاء الاطفال الذين تم اختيارهم من المترددين على عيادة امراض الدم بقسم الاطفال بمستشفيات جامعة عين شمس على النمو الطولي لهم و على كثافة املاح العظام.

وقد تم ذلك باعطاء كل طفل 25 جم زنك يوميا بالفم لمدة 12 شهر متواصلة ثم بعد ذلك تم قياس الطول ووضعه على منحنى الطول الخاص بالاطفال المصريين، كما تم قياس معامل (Z) كمؤشر للتغيير في كثافة املاح العظام.

وقد أظهرت النتائج ان اعطاء الزنك له تأثير ايجابي على زيادة النمو الطولي و زيادة كثافة املاح العظام في هؤلاء الاطفال و أن  هناك اختلافا احصائيا واضحا بين الطول و كثافة املاح العظام قبل و بعد اعطاء الزنك.و أظهرت الدراسة و النتائج انه لم يكن هناك اختلافات احصائية واضحة بين الذكور و الاناث فيما يتعلق بالزيادة في النمو الطولي او في مقدار كثافة املاح العظام.كما أوصت الدراسة بأنه يتم تتبع النمو الطولي و كثافة املاح العظام في الاطفال المصابين بانيميا البحر المتوسط وان يتم اعطاء هؤلاء الاطفال عنصر الزنك في صورة دواء.

الكلمات الكاشفه:زنك - انيميا البحر المتوسط - عمر ما قبل البلوغ - النمو الطولي - هشاشه العظام

Introduction

Thalassemia ismonogenetic, hereditary hematologic disorders, inherited as an [autosomal recessive](http://en.wikipedia.org/wiki/Autosomal_recessive) [blood disorder](http://en.wikipedia.org/wiki/Blood_disorders), characterized by abnormal formation of [hemoglobin](http://en.wikipedia.org/wiki/Hemoglobin)and presenting as [microcytic anemia](http://en.wikipedia.org/wiki/Microcytic_anemia)[1].Thalassemic patients have unbalanced globin chain synthesis with ineffective erythropoiesis and increased peripheral hemolysis [2].Expansion of bone marrow cavity, decreased cortical and trabecular bone tissues and osteoporosis are commonly seen in these patients[3]. Symptoms include [fatigue](http://health.nytimes.com/health/guides/symptoms/fatigue/overview.html), [shortness of breath](http://health.nytimes.com/health/guides/symptoms/breathing-difficulty/overview.html), bone deformities in the face, growth failure and yellow skin [4].Signs are usually linked to[iron overload](http://en.wikipedia.org/wiki/Iron_overload), infection, bone deformities, [enlarged spleen](http://en.wikipedia.org/wiki/Splenomegaly), slowed growth rates, andheart problems [5].

Pathogenesis of osteoporosis in thalassemic patients is multi-factorial.Bone marrow expansion due to ineffective erythropoiesis results in reduction of trabecular bone tissue[6].Iron deposition directly in the bone impairs osteoid maturation and inhibits mineralization.Use of iron chelators as desferrioxaminecan lead to lower serum calcium, magnesium and higher phosphorusand parathyroid hormone level levels[7].Endocrine dysfunction consisting mainly of hypogonadism in addition to hypothyroidism, hypoparathyroidism can impair osteogenesis[8].Reduced physical activity as a result of the disease complications and parental over-protectiveness can worsen the condition[9].Growth failure is usually noticed in thalassemics[10]. It could be attributed tochronic anemia, transfusion-related iron overload, and chelation toxicity.Other contributing factors include hypothyroidism, hypogonadism, growth hormone deficiency/insufficiency, chronic liver disease, undernutrition, and psychosocial stress [11]. Malnutrition, inadequate nutrient intake (zinc, folic acid, vitamin D, carotenoids, and retinol binding proteins)may play a role in growth retardation in these children[12].

Bone mineral density(BMD) is defined clinically as the amount of bone minerals- mostly calcium and phosphorus-expressed in grams in a given area of bone, expressed in square centimeters[13].BMD is measured by Dual-energy X-ray absorptiometry (DEXA) which is considered to be the most standardized form and widely used technique due to its ease of use, precision, accessibility and low cost, in comparison to other modalities of BMD measurement. DEXA can measure as little as 2% of bone loss per year. It is fast and uses very low doses of [radiation](http://www.webmd.com/cancer/what-to-expect-from-radiation-therapy)[14].

Densitometry reporting is done either by using T-score in which BMD is compared to the average score of a healthy 30-year-old person, or Z-score in which BMD value is compared to thata healthy personof the same age, [sex](http://men.webmd.com/guide/7-sex-mistakes-men-make), and race as the examined person [15].

Zinc is trace element and a micronutrient of outstanding and diverse biological and clinical importance .Zinc ions have catalytic, structural, and regulator functions[16].Zinc is an essential trace element to the structure and function of bone and its metabolism [17].Itis an essential for all the steps of osteogenesis,including the production of the extracellular organic matrix (osteoid),the mineralization of the matrix to form bone; and bone remodeling by resorption and deposition. [18].Accordingly, zinc supply can have a positive impact on both bone mineral density and linear growth [19].

Aim of the study:To study the effect of zinc supplementation on linear growth and bone mineral density in prepubertal children with beta- thalassemia major.

Subjects and methods

Study population

This intervention study was conducted on forty prepubertalthalassemic children with beta-thalassemia major,19 males (47.5%) and 21 females (52.5%).Their age ranged from 6.2-to 10.8 years (mean age 8.99 ± 1.32 years). Children were recruited from the regular attendants of Hematology clinic, Department of Pediatrics, Children hospital, Ain Shams University and work was completed in Institute of Postgraduate Childhood Studies, Ain Shams University.The study started at April 2012 and continued until April 2014.All selected children fulfilled the following inclusion criteria:age between 6 and 10 years,diagnostic criteria of β- thalassemia major,history ofrepeated blood transfusion and receiving chelating therapy,osteoporosis as shown by DEXA (Z-score<-2.5) ,normal serum calcium and no bisphosphonates therapy.

An informed consent was obtained from parents after full explanation of the aim of the study and nature of the work.Also approval of the ethics committee of the university was taken.

Methods

All children were subjected to full history taking, full comprehensive medical examination and pubertal developmentasssessment.Venous blood sampleswere taken to measure serum zinc level. Blood samples were collected in ice boxes to the Community and Public Health Department laboratory where serum zinc level measurement was carried out in the atomic absorption laboratory using the atomic absorption spectrometer Autosampler Model A 600)Serum zinc values <80 µg/dl are considered hypozincemia[20]. The degree of hypozincemia was suggested to be classified according to serum zinc level Degree of hypozincemia was classified according to serum zinc level (table 1).

Table (1): Degree of hypozincemia in relation to serum zinc level

|  |  |
| --- | --- |
| Degree of hypozincemia(<80 µg/dl) | Serum zinc level(µg/dl) |
| Mild | 70 - <80 µg/dl |
| Moderate | 60 - <70 µg/dl |
| Severe | 50 - <60 µg/dl |

Height and weight were recorded prior to DEXA scanning. Both were plotted on the Egyptian percentile growth charts for stature and body mass index (BMI) [21]. Z score of the spine was recorded as a measure of BMD.

BMD Z -score from 2.5 to -1 was considered normal,BMD Z -score from < -1 to -2.5 was considered osteopenia andBMD Z-score < - 2.5 was considered osteoporosis[22].

All the patients undergoing this study were osteoporotic with Z-score < - 2.5. A new classification of osteoporosis was suggested in order to facilitate the assessment of changes in BMD after zinc supplementation. Osteoporosis was classified as shown in table (2).

Table (2): Degree of osteoporosis according to BMD Z-scoring.

|  |  |
| --- | --- |
| Degree of osteoporosis (<-2.5 SD) | Z-scoring |
| Mild | <-2.5 to -3 |
| Moderate | <-3 to -3.5 |
| Severe | <-3.5 |

Prior to zinc supplementation CBC,serum ferritin,ALT,serum calcium and hemoglobin electrophoresis were obtained by reviewing the patients records. BMI was also recorded.

Zinc was provided to the selected patients in the form of zinc capsules (vita zinc 25 mg once daily).After 12 month of zinc supplementationeach patient was subjected to evaluation of serum zinc,DEXA scanning to measure BMD Z- score, putting in consideration to use the same machine used in primary BMD assessment to avoid soft ware differences between machines, which might give inaccurate resultsandheight percentile was measured and plotted in the same way as before zinc supplementation.

Statistical analysis:

Data obtained from the research will be organized, tabled and analyzed with the help of SPSS/PC. Categorical data were presented as frequencies (n) and percentage (%). Pearson Chi-Square was used to analyze categorical data.P value was calculated and P value less than 0.05 was considered statistically significant. Information and statistical data were provided by IT and, Institute of Postgraduate Childhood Studies

Results

Table(3): Frequency distribution of patients regarding their height percentile beforeand after zinc supplementation

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | Before zinc supplementation | | After zinc Supplementation | |
| N | % | N | % |
| 5th-<10th | | 12 | 30.00 | 6 | 15.00 |
| 10th-<25th | | 19 | 47.50 | 18 | 45.00 |
| 25th-<50th | | 9 | 22.50 | 14 | 35.00 |
| 50th-<75th | | 0 | 0.00 | 2 | 5.00 |
| Total | | 40 | 100.00 | 40 | 100.00 |
| Chi-square | X2 | 5.93 | | | |
| P-value | 0.115 | | | |

Before zinc supplementation 77.5% of patients have less than 25th height percentile. The figure dropped to 60% after zinc was provided. No patients recorded 50th height percentile or more before zinc was given and 5% exceeded 50th percentile after zinc supplementation.

Table (4): Comparison of height, serum zinc level, and BMD Z-scoring, before and after zinc supplementation in the total sample.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | | | | | Paired Samples Test | |
| Range | | | Mean | ± | SD | t | P-value |
| Height (cm)  before zinc supp. | 114.15 | - | 139.35 | 121.30 | ± | 12.64 | -11.512 | <0.001\* |
| Height (cm)  after Zinc supp. | 118.90 | - | 150.10 | 128.80 | ± | 13.92 |
| Serum zinc(μg/dl)  before zinc supp. | 52.000 | - | 86.000 | 67.925 | ± | 6.896 | -6.325 | <0.001\* |
| Serum zinc(μg/dl)  after zinc supp. | 56.000 | - | 81.000 | 70.250 | ± | 6.348 |
| BMD Z-Score (SD)  before zinc supp. | -3.900 | - | -2.600 | -3.008 | ± | 0.410 | -15.981 | <0.001\* |
| BMD Z-Score (SD)  after zinc supp. | -3.700 | - | -1.800 | -2.465 | ± | 0.496 |

There was statistically significant difference when mean serum zinc level, mean height and mean BMD Z-score were measured before, and after zinc supplementation for 12 months (P value <0.001)

Before zinc was provided, the height ranged between 114.15 and 139.35cm (mean 121.30±12.64 cm). After zinc was given for one year, the height ranged between 118.90 and 150.10 (mean 128.80 ± 13.92 cm) .

Serum zinc level was measured prior to zinc supplementation.Serum zinc level ranged between 52μg/dl and 86μg/dl (mean 67.925 ± 6.896 μg/dl). Serum zinc was measured after zinc supplementation for one year. Serum zinc level ranged between 56 μg /dl and 81μg/dl (mean 70.250 ± 6.348 μg/dl).

Before zinc supplementation BMD Z- score for the patients in the study sample ranged between -3.9 and -2.6 (mean -3.008 ± 0.410). After zinc was supplemented for one year, Z-score ranged between -3.7 and -1.8 (mean -2.465 ± 0.496).

Table (5):Comparison of height, serum zinc level, and BMD Z-scoring, before and after zinc supplementation in both males and females.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Gender | | | | | | t-Test | |
| Female | | | Male | | |
| Mean | ± | SD | Mean | ± | SD | t | P-value |
| Height .(cm)  before zinc supp. | 122.34 | ± | 12.22 | 120.00 | ± | 11.543 | 7.765 | 0.345 |
| Height.(cm)  after Zinc supp. | 129.55 | ± | 12.657 | 127.59 | ± | 12.005 | 7.167 | 0.269 |
| Serum zinc before zinc  supp. (μg/dl) | 66.429 | ± | 6.226 | 69.579 | ± | 7.381 | -1.464 | 0.151 |
| Serum zinc after zinc supp.(μg/dl) | 69.810 | ± | 6.577 | 70.737 | ± | 6.226 | -0.457 | 0.651 |
| BMD Z-Score before zinc supp.(SD) | -2.971 | ± | 0.366 | -3.047 | ± | 0.461 | 0.579 | 0.566 |
| BMD Z-Score after zinc  supp.(SD) | -2.400 | ± | 0.460 | -2.537 | ± | 0.537 | 0.868 | 0.391 |

There was no statistically significant difference between males and females when mean height, serum zinc level and BMD Z-score were measured before and after zinc supplementation (P value> 0.05).

Table (6): Mean height,serum zinc level and BMD Z-score before and after zinc supplementation in males.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Before zinc supp. | After zinc supp. | t | P value |
| Mean height(cm) | 120±11.543 | 127.59±12.005 | -11.231 | < 0.001\* |
| Mean serum zinc level (μg/dl) | 69.579±7.381 | 70.737±6.226 | -6.002 | < 0.001\* |
| Mean Z score (SD) | -3.047±0.461 | -2.537±0.537 | -12.762 | < 0.001\* |

There was statistically significant difference in males when mean serumzinc, height and BMD Z-score were measures before and after zinc supplementation (P value <0.001).

Table (7): Mean height,serum zinc level and BMD Z-score before and after zinc supplementation in females.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Before zinc supp. | After zinc supp. | t | P value |
| Mean height(cm) | 122.34±12.22 | 129.55±12.657 | -11.584 | < 0.001\* |
| Mean serum zinc level (μg/dl) | 66.429±6.226 | 69.810±6.577 | -6.221 | < 0.001\* |
| Mean Z-score (SD) | -2.971±0.366 | -2.400±0.460 | -12.612 | < 0.001\* |

There was statistically significant difference in females when mean serumzinc, height and BMD Z-score were measures before and after zinc supplementation (P value <0.001).

Table (8): Male and female mean values for serum hemoglobin, WBCs, platelets, serum ferritin ,calcium, ALT, and hemoglobin electrophoresis before zinc supplementation.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Gender | N | Mean | ±SD | t | P value | sig. |
| WBC(×10³/ml) | M | 19 | 7.4 | 2.7 | 1.052 | 0.282 | NS |
| F | 21 | 6.9 | 2.1 |
| PLT.(×10³/ml) | M | 19 | 320.2 | 190.2 | 1.974 | 0.061 | NS |
| F | 21 | 331.4 | 195.4 |
| Hb(gm/dl) | M | 19 | 6.2 | 0.6 | 2.615 | 0.595 | NS |
| F | 21 | 6.8 | 0.6 |
| Serum ferritin(ng/ml) | M | 19 | 3755.5 | 2011.2 | 0.541 | 0.601 | NS |
| F | 21 | 3659.4 | 2056.4 |
| ALT(iu/L) | M | 19 | 49.7 | 22.9 | 0.079 | 0.922 | NS |
| F | 21 | 50.2 | 24.4 |
| Serum calcium(mg/dl) | M | 19 | 9.79 | 0.59 | 2.822 | 0.625 | NS |
| F | 21 | 9.92 | 0.61 |
| Hb.elecroph.  Hb.F % | M | 19 | 56.77 | 26.4 | 0.082 | 0.982 | NS |
| F | 21 | 54.51 | 23.6 |
| BMI | M | 19 | 19.4 | 10.8 | 0.455 | 0.422 | NS |
| F | 21 | 19.6 | 10.9 |

Before zinc supplementation there was nostatistically significant difference between males and femalesregarding the mean values for serum hemoglobin, WBCs, platelets, serum ferritin , calcium, ALT, and hemoglobin electrophoresis (P value> 0.05).

Discussion:

In the present study the impact of zinc supplementation on linear growth and bone mineral density in prepubertalthalassemic children was evaluated.Serum zinc level was measured prior to zinc supplementation.Serum zinc level ranged between 52μg/dl and 86μg/dl (mean 67.925 ± 6.896 μg/dl). Ninety five percent of the patients undergoing this study showed low serum zinc level (less than 80μg/dl) ,and only five percent showed normal level (≥ 80μg/dl).These findings come near to those obtained by many authors[23-25].

With respect to reference cut-off point of serum zinc level (80 μg/dl), 27.5% of patients in this study presented with mild zinc deficiency, with serum zinc level ranging between 70μg/dl and 79μg/dl. Those presented with moderate zinc deficiency (60-69μg/dl) were %62.5. Severe deficiency (50-59μg/dl) was reported in only 5% of patients.

Although Keikhaei et al, 2010 showed hypozincemia in 50 % of their patients, 20% of their patients had severe zinc deficiency[26]. This might be because older patients were involved in their study, with mean age 15±5 years.

Many studies reported decreased serum zinc level in thalassemic patients.Arcasoy et al, (2001)reported that chronic Zn deficiency occur in the patients with thalassemia major (TM), but they stressed on the importance of measuring serum zinc binding capacity (ZnBC) to evaluate body zinc status. They postulated that Zn deficiency in TM may be due to hyperzincuria, high ferritin levels, hepatic iron load and hepatic dysfunction. The study has been carried out on 30 TM patients. As control group, 13 healthy children were involved. Serum Zn and ZnBC were determined by atomic absorption, then saturation index (SI%: serum Zn/ZnBC x 100) was calculated. Serum Zn levels in all patients were lower than control (p < 0.01). Serum ZnBC was found to be lower in TM patients than control (p < 0.01).

While serum Zn levels decrease and ZnBC increase in nutritional Zn deficiency, serum Zn levels decrease but ZnBC doesn't increase in patients with thalassemia[23].

Tabatabei et al, (2003) reported that 84% of ß-thalassemia major patients had zinc deficiency[27].Fikry et al, (2003) found apositive correlation between serum level and height/age[24].

Bekheiia et al,( 2004), reported that low serum zinc was found in 84.8% of their patients. Hypozincemia was severe in 44.7% of them. Patients under this study were aged 10–20 years. The above mentioned study might suggest that the severity of hypozincemia increases with age .This probably might pay the attention for early zinc supplementation to avoid the negative impact of zinc deficiency in older age[28].

Mahyar et al, (2010) in their study proved low serum zinc level in thalassemic children[29].Keikhaei et al,( 2010)showed hypozincemia in 50 % of their patients in a similar study[26].Sherief et al, (2014), showed significantly lower level of zinc in thalassemic group than controls[25].

Contrary to the results of the former studies, Kosarian et al, (2000) and Reshadat et al,( 2006)found that serum zinc level in their thalassemic patients and controls was within normal limits[30, 31].

Mehdizadeh et al,( 2008)found that zinc deficiency in thalassemic patients who are on regular blood transfusion is rare[32].

Before zinc supplementation BMD Z- score for the patients in the study sample ranged between -3.9 and -2.6 (mean -3.008 ± 0.410). After zinc was supplemented for one year,BMD Z-score ranged between -3.7 and -1.8 (mean -2.465 ± 0.496).The difference between mean BMD Z- score before and after zinc supplementationwas statistically significant (P value <0.001).

The mean BMDZ-score before zinc was provided, was in the moderate osteoporosis category (-3.008± 0.410). After zinc supplementation this mean became no longer in the osteoporotic side and moved to the osteopenic side (-2.465± 0.496).

This in turn can reflect a positive impact of zinc supplementation on these osteoporotic patients. It is remarkable that 67.5% of cases became no longer osteoporotic and had their Z-score more than -2.5 (osteopenia).AlthoughBMD Z-scoring for 67.5 % of the patients in this study moved from osteoporosis to osteopenia (63.2% of males and 71.4% of females had their BMD Z-scoring moving from osteoporosis to osteopenia), none of our patients had a normal BMD Z- score at the end of the study. This probably could have been achieved if we start giving zinc earlier and /or if we continue giving zinc for a longer period.

It was also remarkable that zinc intake improved BMD Z-scoring in males and females more or less indifferently.

Leung et al, (2009) reported that 62% of their thalassemic patients showed low BMD Z -score than normal[33].Pirinççioğlu,( 2011) found significantly lower BMD findings in ß – thalassemic children in comparison to their peers[34].

Bekheiia et al, (2004) reported low serum zinc levels in 84.8% of the cases of their study compared to controls. They reported decreased BMD in 68.7% of these patients[28].

Izadyar et al, (2012) found that at least 50% of their thalassemic patients suffered from some degree of bone mineral loss, either osteopenia or osteoporosis[35].

Fung et al, (2013)came to the conclusion that if zinc supplementation is found to have a clinically important effect, this simple, safe, non-invasive therapy could quickly become a part of the standard care of these young patients and improve overall health in children and adult patients with ß-thalassemia[36].

Before zinc was provided, theheight ranged between 115.15 and 139.35 cm (Mean 121.30 ± 12.64 cm). After zinc was given for one year, the height ranged between 118.90 to 150.10 cm (Mean 128.80± 13.92 cm). The difference in mean height before and after zinc was supplemented was statistically significant (P value <0.001).

Males and females look to react indifferently to zinc supply regarding their mean height change after zinc supplementation.

Arcasoy et al, (1987) studied Effects of zinc supplementation on linear growth in β –thalassemia.They demonstrated that zinc deficiency is one of the factors responsible for retarded linear growth in beta-thalassemia major. Only the patients who received zinc supplementation showed an acceleration of growth in height[23].

Faranoush et al,( 2008).In their studycame to the conclusion that oral zinc sulfate has no significant effect on linear growth of β- thalassemia patients[37].

conclusion:

Zinc supplementation for one year for prepubertalthalassemic children can have a positive impact on their linear growth as well as their bone mineral density.

There is statistically significant difference on measuring mean serum zinc level, height and BMD Z-score before and after zinc supplementation.

Recommendations:

Zinc supplementation to prepubertalthalassemic children is advised to improve their BMD. This in turn can improve their bone strength and quality leading to a better quality of life.Furthermore,providing zinc to thalassemic children may improve their height velocity, and in turn their final stature.

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