

Zinc and Copper Status in Children with *Beta-Thalassemia Major*

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Received: Sep 02, 2009; Final Revision: Jan 06, 2010; Accepted: Mar 10, 2010

Abstract

Objective: There are some reports in which a condition of zinc deficiency and its associated outcomes with a change in concentration of serum copper among the thalassemic patients has been highlighted. The aim of this prospective study was to determine the serum zinc and copper levels in children with beta-thalassemia major.

Methods: In this cross sectional study all children under 12 years affected by beta thalassemia major (40 patients) were evaluated for serum zinc and copper levels in Qazvin thalassemia center (Qazvin, Iran) in 2007. Serum measurements for zinc and copper were performed by atomic absorption spectrophotometer.

Findings: The mean concentrations of serum zinc and copper levels were 67.35 ± 20.38 and 152.42 ± 24.17 $\mu\text{g/dl}$ respectively. Twenty-six (65%) of thalassemic patients had zinc concentration under 70 $\mu\text{g/dl}$ (hypo-zincemia). None of the thalassemic children had copper deficiency. No significant correlation between serum zinc level with age, weight, height, body mass index, duration of blood transfusion, desferrioxamine dose and ferritin level was observed in thalassemic patients ($P=0.3$).

Conclusion: This study revealed that hypo-zincemia is common in thalassemic patients, but in contrast, there is no copper deficiency. Further evaluation in this regard is recommended.

Iranian Journal of Pediatrics, Volume 20 (Number 3), September 2010, Pages: 297-302

Key Words: Beta-thalassemia; Zinc; Copper; Children

Introduction

Thalassemia is the most common hereditary anemia in human^[1,2]. This disease was

initially described by Cooley and Lee^[1,2]. Almost 150 million people carry the thalassemia gene universally and it is more common in Mediterranean regions than

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anywhere in the world^[3,4]. The most common types of disease are the alpha and beta thalassemia. Beta thalassemia major is the most severe form requiring repeated blood transfusions and desferrioxamine injections. Although such treatments increase the patients' life span, on the other hand a variety of complications, including endocrine, metabolic, skeletal and growth disorders are being observed due to the high contents of iron storage in the body^[5,6]. Zinc is one of the essential micronutrients in human and acts as a cofactor for more than 300 enzymes and plays a particular role in human growth and development^[7].

Likewise, the copper is considered an important micronutrient with highest amount in liver, brain, heart, and kidneys. Copper is also an essential structural co-participant of many enzymes acting as cofactor in majority of enzymatic reactions including those of cytochrome C oxidase, lysyl oxidase, superoxide dismutase, and tyrosinase^[4,8]. In some reports it has been described that the patients with beta thalassemia major suffer from zinc deficiency which could be seen as one of the causes of delayed maturity in thalassemic patients^[7,9,10].

Also there are reports indicating a change in serum level of copper in patients with thalassemia major^[9,11]. Shamshirsaz et al found lower serum copper concentration while Kajanachumpol et al found higher copper concentration^[9,11].

In Iran there are more than 20,000 thalassemia major patients^[3]. We have conducted this study to evaluate zinc and copper status in children observed in Qazvin thalassemia center (Qazvin, Iran).

Subjects and Methods

In this prospective cross sectional study all children under 12 years affected by beta thalassemia major (40 patients) that were covered by Qazvin thalassemia center, were

evaluated for serum zinc and copper levels from September to November 2007 (Census sampling). Inclusion criteria were: 1) age under 12 years; 2) confirmation of beta-thalassemia major by hemoglobin electrophoresis. Children above 12 years old and other hemoglobinopathies were excluded from the study. Demographic and anthropometric data and history of disease and treatment were collected by physical examination, medical records and laboratory measurements.

Weight and height were measured by using standard methods by corresponding pediatrician. Weight measurement was performed using Seca scale with a precision rate of 100gr with no shoes and minimum covering.

The height, while in standing position, was measured from head to heel using metal scale with a precision rate of one cm. The validity and reliability of instruments were checked on a regular basis. Since there is standard international serum values for zinc and copper in children, so the control group is no more needed. The normal value ranges for serum zinc and copper were 70-120 μ g/dl and 70-150 μ g/dl respectively (Tietz Textbook of Clinical Chemistry, 2001). Written permission of the parents to take 5 ml blood sample for determination of serum levels of zinc and copper were obtained following a clear full oral explanation of the subject of research. The blood samples were transferred into labeled acid-washed tubes and centrifuged at 2500 rpm aseptically. The serum samples were removed using acid-washed tips and kept at -20°C until use. Later, the samples were transferred to the Biochemistry Department at Iran Atomic Energy Organization in Tehran. The serum contents of both zinc and copper were measured by Flame Atomic Absorption Spectrophotometer (AAS) technique using Varian Spectra 220 Instrument (Australia). All tests were performed in triplicate. Hemoglobin was measured by Sysmex apparatus (k-800) and ferritin of serum (Pishtaz teb, Tehran, Iran) by Elisa method. It should be emphasized that the kidney and liver function tests were within normal

limits in all patients. Patients were divided into 2 groups, based on the serum value of zinc and copper (less and more than 70 $\mu\text{g}/\text{dl}$) and variables such as age, height, serum ferritin, etc compared in both groups. The data were recorded and analyzed by t-test. *P*-value <0.05 was considered as significant.

Ethical Considerations: All parents were given clear explanations regarding the methodology of the research. The present study was ethically confirmed by ethical committee of research department of Qazvin University of Medical Sciences. The children were included in the study if their parents agreed and signed the consent form.

Findings

Out of 40 children with beta thalassemia major 17 (42.5%) cases were males and 23 (57.5%) females. The minimum age was 18 and the maximum 144 months with a mean age of 96.75 \pm 40.99 months. The minimum, maximum and mean weight, height and body mass index (BMI) in thalassemic patients were 11, 36, 22.96 \pm 6.88kg; 79, 138, 118.27 \pm 18.01cm; and 12.40, 20.35, 16.13 \pm 2.03 kg/m² respectively. The minimum and maximum duration of blood transfusion was 12 and 132 months respectively with a mean duration of 85.67 \pm 38.60 months. The minimum and maximum interval between two blood transfusions was 10 and 30 days, respectively with a mean interval of 21.07 \pm 5.81 days.

The minimum hemoglobin concentration

was 7.1 and the maximum 10.60g/l with mean concentration of 8.91 \pm 0.71g/l. Also the minimum, maximum, and the mean concentrations of serum ferritin were 609, 6985, and 1627.02 \pm 1118.62 ng/ml respectively. The minimum serum concentration of zinc in thalassemic patients was 36 and the maximum 140 with a mean concentration of 67.35 \pm 20.38 $\mu\text{g}/\text{dl}$. Sixty five percent of patients had hypozincemia (Table1). The minimum, maximum, and the mean concentration of serum copper in patients were 100, 200.5, and 152.42 \pm 24.17 $\mu\text{g}/\text{dl}$, respectively. None of the patients showed a copper concentration lower than normal (Table1).

There was no significant difference between serum ferritin level and the mean serum concentrations of zinc and copper (Table 2). Also there was no significant relation between serum zinc level of thalassemic patients with age, weight, height, BMI, duration time of blood transfusion, desferrioxamine dose and ferritin level (*P*=0.3)(Table 3).

Discussion

This study showed that in thalassemic patients hypozincemia is common but there is no copper deficiency. The thalassemia major is the severe form of the beta thalassemia disease and the patients need repeated blood transfusions and chelation therapy to continue their lives. Although by new therapies the patients' lifespan has

Table1: Serum zinc and copper concentrations in thalassemic patients

Trace elements	Value	Number
Serum zinc ($\mu\text{g}/\text{dl}$)	Less than normal (<70)	26 (65%)
	>70 Normal	14 (35%)
	Total	40 (100%)
Serum copper ($\mu\text{g}/\text{dl}$)	Normal (<70)	0
	>70	40 (100%)
	Total	40 (100%)

Table2: The relationship between serum ferritin level and the mean serum concentrations of zinc and copper in children with beta thalassemia major

Trace elements	Serum ferritin (ng/ml)	No	Serum (μ g/dl)	P value
Zinc	<1000	5 (12.5%)	63.20 \pm 16.74	0.6
	>1000	35 (87.5%)	67.94 \pm 20.99	
Copper	<1000	5 (12.5%)	156.10 \pm 34.49	0.7
	>1000	35 (87.5%)	151.90 \pm 22.98	

increased to 4th and 5th decade, however these patients are subject to a variety of complications such as growth impairment, endocrinopathy, hypogonadism and so on^[1,2]. Although the role of iron accumulation in appearance of these complications is well documented, there are some reports emphasizing the role of zinc and copper associated with such clinical problems^[12-16]. Zinc is one of the essential micro-nutrients in human and considered as the most important mineral preceded by iron. It acts as the cofactor of more than 300 enzymes. Zinc deficiency leads to several clinical disorders including the growth impairment, hypogonadism, osteoporosis, osteopenia, immunologic disorders, repeated infections, etc^[7].

Tabatabaei et al reported that 84.8% of thalassemic major patients had zinc deficiency. They emphasized that the cause of zinc deficiency in these patients was due

to insufficient zinc of dietary intake^[17]. Yazdiha et al showed that the serum concentration level of zinc in thalassemic patients (37 \pm 1.9mg/dl) was lower than in control group (51 \pm 1.8) and there was significant difference statistically. They recommended zinc supplement for thalassemic patients^[10].

Similar reports were provided by other researchers^[11,18-23]. Al-Samarrai et al attributed the cause of hypozincemia in thalassemic patients to hyperzincuria resulted from following hemolysis of red blood cells^[21]. Hashemi Poor et al demonstrated that zinc concentration of hair in thalassemic patients (112.7 \pm 53.11 ppm) was lower than that in control group (149.6 \pm 72.21 ppm). They suggested that the etiology of zinc deficiency is malnutrition and inadequate zinc intake. They advise administration of zinc supplement^[24]. On the other hand, Mehdizadeh et al have reported that mean

Table3: The relationship between mean serum concentrations of zinc and different variables in children with beta thalassemia major

Risk factors	Zinc \leq 70 μ g/dl	Zinc $>$ 70 μ g/dl	P value
	Mean (SD) (N=26)	Mean (SD) (N=14)	
Age (mo)	106.07 \pm 36.63	86.57 \pm 41.61	0.1
Weight (kg)	23.88 \pm 66.65	21.25 \pm 7.22	0.2
Height (cm)	121.19 \pm 16.38	112.85 \pm 20.22	0.2
Body mass index (kg/m ²)	15.81 \pm 1.93	16.06 \pm 1.58	0.7
Duration of blood transfusions (mo)	91.65 \pm 36.82	74.57 \pm 40.74	0.2
Number of blood transfusions (per month)	1.6 \pm 0.56	1.71 \pm 0.46	0.7
Ferritin (ng/ml)	1749.15 \pm 1347.42	1400.21 \pm 421.13	0.3
Desferrioxamine dose (mg)	10000.55 \pm 2500	10000 \pm 3000.05	0.9
Hemoglobin (mg/dl)	8.84 \pm 0.68	9.05 \pm 0.76	0.4

serum zinc level was significantly higher in thalassemic group. They noted that zinc deficiency is rare in thalassemia^[25]. Report of Reshadat et al showed that 77% of thalassemic patients have normal serum zinc level and remainder greater than normal. They emphasize that medical treatment of these patients is not appropriate, so the value of zinc administration should be more evaluated^[26]. In contrast to the mentioned studies Kosarian et al reported that serum zinc level in major thalassemic patients and control group were within normal limits, thus these patients are not affected by zinc deficiency^[27]. Present study showed that 65% of thalassemic children have hypozincemia. The causes of zinc deficiency in these patients may be related to insufficient amount of zinc in daily meals, abnormality in urinary absorption of zinc, kidney dysfunction, urinary secretion of zinc, disturbance in zinc metabolism and higher level of zinc excretion in sweat^[1-4].

Because there was no relationship between serum zinc level and different variables such as age, weight, height, BMI, duration of blood transfusion, desferrioxamine dose and ferritin level, so it is most likely that other risk factors unrelated to thalassemia disease such as nutritional status may be responsible for hypozincemia.

Copper is also one of the essential micronutrients of human body mainly attached to albumin and ceruloplasmin. This trace element acts as the cofactor for at least 30 enzymes and many manifestations of copper deficiency and toxicity are associated with irregularities in these enzymes^[4,8]. Some studies showed that there was an increase in serum level of copper in patients experiencing thalassemia major^[11-13,21,23,28]. Al-Samarrai et al concluded that the etiology of hypercupremia is hemochromatosis, which is a principal complication of thalassemia^[21]. However, reports of Bekheirnia^[29], Tabatabaei^[17], Naser^[19] and Eshghi^[22] revealed reduction in serum level of copper. Although study by

Kassab-Chekir showed no change in copper concentration of serum^[20].

The serum concentration of copper in patients with thalassemia major depends on several factors including the amount of copper intake in daily diet, intestinal uptake of copper, iron accumulation, kidney function, copper to zinc ratio, and administration of Desferal^[11,13]. Fortunately none of our thalassemic patients had copper deficiency. This shows that the factors that influence copper level are under control.

The limitations of our study were the small group, local investigation and unavailability of data concerning diet regimens. With respect to importance of identification of zinc deficiency in thalassemic patients for prevention of severe complications such as decreased mineral density of bone^[12,22], we recommend repetition of this study in a larger scale.

Conclusion

This study revealed that hypozincemia is common in thalassemic patients, but there was no copper deficiency. Further evaluation in this regard is recommended. There was no significant difference between serum ferritin level and the mean serum concentrations of zinc and copper in this study.

Acknowledgment

This research was supported by research department of Qazvin University of Medical Sciences (Code 172,173) for which we would like to express our thanks and also best thanks to the personnel of Quds Children's Hospital for their sincere cooperation.

Conflict of Interest: None

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