AL-Qadisiyha Journal For Science Vol.19 No. 4Year 2014
Elham A. ISSN 1997-2490

Comparison Between Zinc, Copper and Iron Levels in Children with Beta Thalassemia Major And healthy Individuals in Najaf City

Receved : 29\12\2013 Accepted : 30\3\2014

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Abstract:

Thalassemia is the most common hereditary anemia in human. 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 deferrioxamine injections.The present study aims to evaluating the serum iron, copper and zinc in thalassemia centre in AL-Zahraa hospital at Najaf city. Forty four patients (age from 3-16 years) with beta thalassemia major (20 males and 24 females) that undergo periodical blood transfusion and they are on deferrioxamine (DFO) as chelating agent were involved in this study. Fifty controls of matched age and gender (25 males and 25 females) were also, included in the study. Results showed that the zinc levels was significantly ($p<0.05$) decreased in beta thalassemia patients when compared with controls, but in contrast there is a significantly ($p<0.05$) increased of iron and copper levels in beta thalassemia major patients when compared with normal control. No significant correlation between serum zinc and copper levels with age, duration of blood transfusion, deferrioxamine dose, only strong relationship between copper and zinc levels and ferritine levels was observed in thalassemic patients.

Key words: zinc, copper, iron, beta thalassemia major

Introduction:

Beta-thalassemia major is an autosomal recessive disease that leads to a severe hemolytic anemia in early infancy[1,2]. Depletion or impaired synthesis of β-globin chain can result in an imbalanced production of globin chains towards higher production of α-chain, which converts hemoglobin from a normal oxygen transporting function into toxic inclusions bodies,causing peripheral erythrocyte hemolysis[1,3,4]. Glutathione decrease is another reason for destabilization of hemoglobin [5,6]. Anemia in β-TM is caused by a combination of ineffective erythropoiesis and premature hemolysis of red blood cells in peripheral circulation. Furthermore, β-TM patients are under continuous blood transfusion leading to iron overload [7]. And also iron overloading as a result of both high plasma iron and high intracellular non hemoglobin iron in β-thalassemias leads to an enhanced generation of reactive oxygen species and oxidative stress [8]**.** This result in producing free radicals and reactive oxygen species (ROS) in the blood cell of thalassemic patients which alter the redox status of these patients and intensification of oxidative stress. [9,10] This leads to congestive heart failure and is one of the most prevalent and important cause of death in beta thalassemia major patients. [11-14]. Beta thalassemia major is the most

severe form requiring repeated blood transfusions and deferrioxamine 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].

Copper is the one of essential trace element present in our bodies. It mostly forms metalloprotiens which act as enzymes. Copper is the major component of hemoglobin which is a protein responsible for oxygen transport in blood cells. It is antibacterial and bears important antioxidant properties. Copper is a central component of the antioxidant superoxide dismutase molecule and also helps in the formation of protein called ceruloplasmin thereby protecting the cells from free-radical injury. Deficiency of this trace element will lead to anemia, neutropenia, and growth impairment, abnormalities in glucose and cholesterol metabolism, and increased rate of infections. On the other hand, an accumulation of copper in body leads to Wilson's disease with copper accumulation and cirrhosis of liver [15].
The zinc is take part in various important body functions including protein synthesis, DNA synthesis, and cellular growth. It is found almost in every cell and plays a vital role in body's immune system affecting innate and acquired immunity. Zinc also has significant antioxidant properties thereby protecting the cells from damage due to free radicals . It is the active site for a number of metalloenzymes which are required for nucleic acid synthesis and also important for other host defense mechanisms like production of monocytes and macrophages and chemotaxis of granulocytes [16]. Zinc is absorbed from small intestine and found in the blood bound to albumin. Impaired growths, alopecia, loss of weight are few of the associated complications due to deficiency of zinc which is one of the factors responsible for growth and puberty disorders in thalassemic patients [17]. Several studies were performed to determine the serum levels of zinc and copper in beta thalassemia major children[12,18,19], that revealed the hypozincemia is common in thalassemic patients, but there is no copper deficiency . Another study was carried out to evaluate the serum copper and zinc in Jordanian thalassaemic patients. Forty two patients with β-thalassemia major on periodical blood transfusion and Defferioxamine were included in this study [16]. Forty age- and gender-matched healthy controls were included in the study. The results indicate that copper and zinc levels were significantly increased in beta thalassemia major patients compared with controls. These finding may be explained by the decreasing rate of glomerular filtration of zinc seen in chronic hemolysis and the disturbance in the metabolism of zinc and copper in thalassaemic patients due to the increasing serum zinc. The high level of copper could be due to increase absorption of copper from gastrointestinal tract [20]. The present study aimed to evaluate the levels of iron, copper and zinc in the serum of Najaf city patients with beta thalassemia major treated with defferioxamine for evaluating the effect of defferioxamine in chelating trace elements copper and zinc.

Material and methods:

This study was carried out among 94 children from Najaf city belonging to different social levels, whose age was(3-16 years). We examined two groups of children, one with beta thalassemia major (n=44,20 males, 24 females) and the other one as controls(n=50, 25 males,25 females). patients were receiving regular transfusion and chelation therapy(defferioxamine DFO) 20-60 mg/kg/d. The study was approved by the thalassemic center in AL-zahraa hospital in Najaf governort. Informed consents were taken from all subjects or their parents prior to participation in the study. Exclusion criteria included use of vitamins and presence of acute illness. Fife milliliters blood was obtained after 8-12h fasting from each subjects, was done just before the transfusion. The blood samples were centrifuged at 3000rpm for 10 minutes and sera were kept at -20°c until analysis. The serum content of iron, zinc and copper were measured by flame atomic absorption spectrophotometry (AAS) technique using Vrian spectra 220 instrument (Australia).

Description data were analyzed by mean and standard deviation the differences in the in the continues variables were compared by using the paired t-test (spss for window version 17.0).A P value OF (<0.05) was considered statistically significant. Correlation coefficient were according to the person function.

Result and discussion:

The hematological and ferritin concentration results of the examined patients and the control group are shown in table (1). It is clear from the result that a significant decrease ($p<0.05$) of hemoglobin concentration (7.1± 1.2g/dl) was noticed in comparison with controls (13.3±1.4 g/dl). On the other hand ferritin concentration was significantly ($p<0.05$) higher in beta thalassemia major patients (2804.52±1367.2µg/l) in comparison with controls (62.7±22.4 µg/l). As shown in table (1) a significant difference in Fe, Zn and Cu levels was observed between patients and the control group ($p<0.05$). Serum iron level was found to be (165.7±20µg/dl) among beta thalassemia major cases, and this value was found to be statistically higher compared to the controls (106.3±15µg/dl).The Cu levels was higher in patients than those of controls (169.7±24µg/dl), (104.88 ±34µg/dl) respectively. Serum Zn level was lower in thalassemia patients (70.2±11.3µg/d) than controls (122.3 ±28µg/dl).

There was a significant relation between serum ferritin level and the mean concentration of zinc and copper r = 0.8,0.75 respectively show fig (1) and (2).

Also there was no significant difference between serum zinc and copper levels of thalassemic patients with age show fig (3)and(4) ,duration time of blood transfusion, defferrioxamine dose and show table (2).

Table (1): Biochemical data (mean ± SD) in children with beta thalassemia major and the control group

Parameters	Thalassemia major group (n=44)	Control group n=50	P value
Hemoglobin g/dl	7.1± 1.2	13.3±1.4	P<0.05
Ferritin µg/L	2804.52±1367.2	62.7±22.4	P<0.05
Serum iron µg/dl	165.7±20	106.3±15	P<0.05
Zinc µg/dl	(70.2±11.3µg/d)	122.3 ±28	P<0.05
Copper µg/dl	169.7±24µg	104.88 ±34	P<0.05

Table (2): results of univariate analysis of serum zinc and copper levels and some parameters in patients with beta thalassemia major

Parameters	Copper mg/dl		Zinc mg/dl	
	r	P value	r	P value
Age	0.16	N.S	0.20	N.S
Duration time of blood transfusion	0.18	N.S	0.32	N.S
Defferrioxamin dose	0.34	N.S	0.37	N.S
Serum ferritin	0.80	<0.005	0.75	

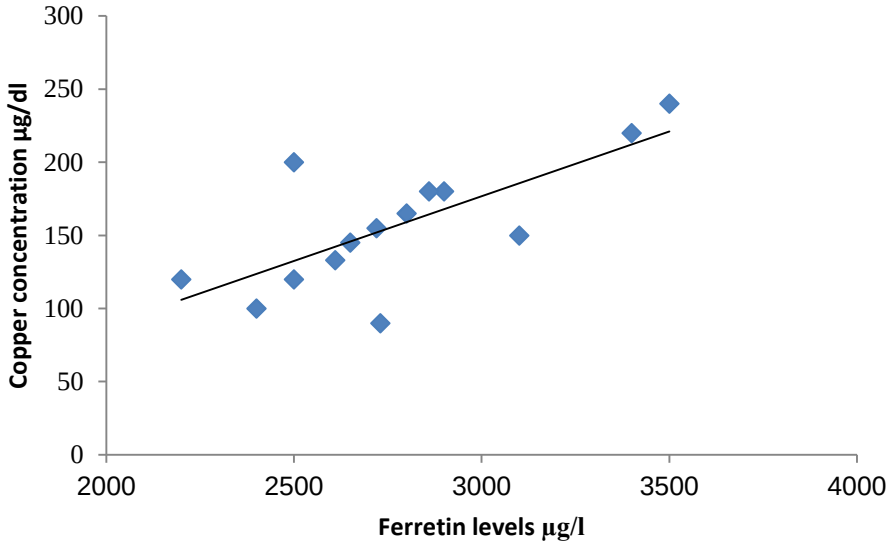
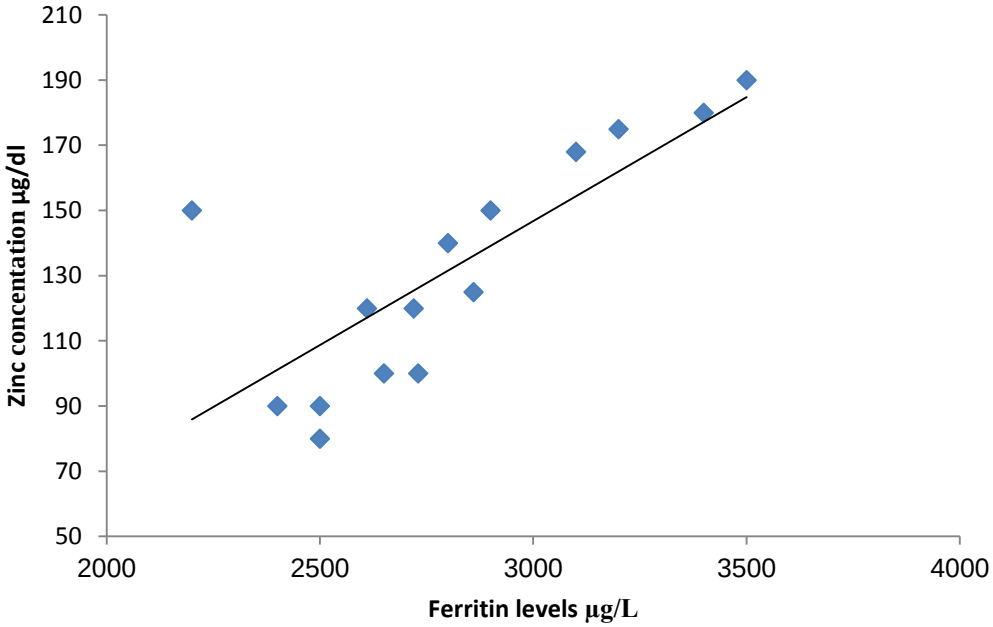
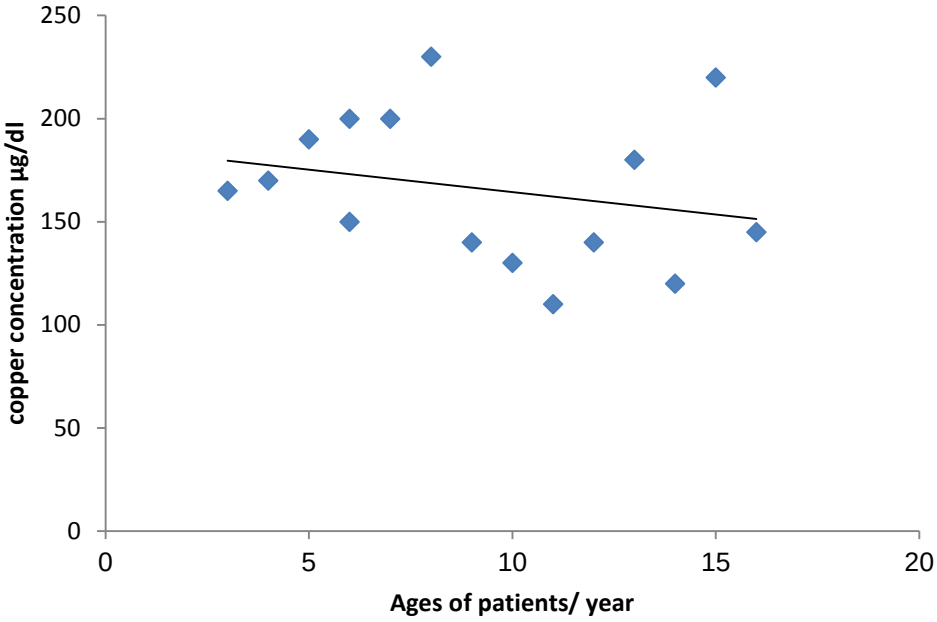


Fig (1) : the correlation between serum copper concentration and ferritin levels in beta thalassemia patients



Fig(2): The correlation between serum zinc concentration and ferritin levels in beta thalassemia patients



Fig(3): The correlation between age and serum copper concentration in patients with beta thalassemia major

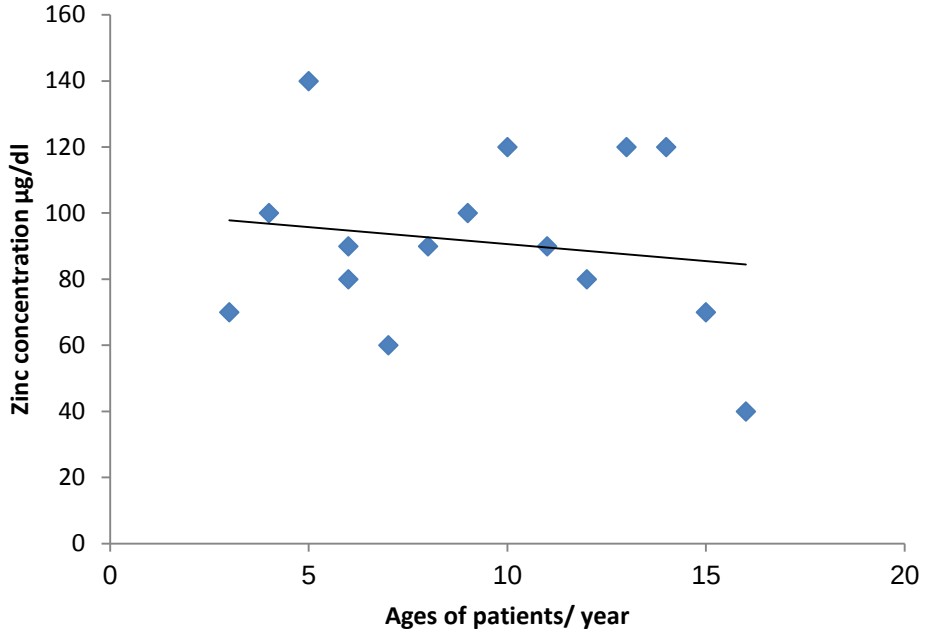


Fig (4): The correlation between age and zinc serum concentration in patients with beta thalassemia major

Patients with thalassemia are known to have poor growth, altered puberty, and immune function as well as reduced bone mineral acquisition .The etiology of these comorbidities is typically ascribed to the toxic effects of transfusion related iron-overload[21]. A rise in iron indices observed in the beta thalassemic patients may be due to erythrocyte hyperhemolysis and to chronic blood transfusion. Similar results were found The significant increase of serum ferritin in the patients indicated an existing iron overload. The acute iron overload found in beta thalassemia can lead to the accumulation of an abnormal molecular iron form (non-transferrin-bound: NTBI). NTBI has hepato and cardio-cytotoxic properties [3]. Furthermore, NTBI contributes to the formation of free radicals and increases hemolytic process. The released iron could play a central role in the oxidation of membrane cells and senescent cell antigen formation, one of the major pathways for erythrocyte removal [22]. The present study investigated the relationship between copper and zinc levels in patients with beta Thalassemia major and the dose of treatment with deferrioxamine DFO as chelating agent, that revealed no significant relation between them, due to the zinc deficiency can cause other disorders in thalassaemic patients, such as inadequate protein-energy status, and it also plays a role in the pathogenesis of deferrioxamine DFO neurotoxicity [5].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 increased to 4^{th} and 5^{th} decade, however these patients are subject to a variety of complications such as growth impairment, endocrinopathy, hypogonadism and so on[23,24], there are some reports emphasizing the role of zinc and copper associated with such clinical problems[25-27]. Different levels of trace elements (zinc and copper) in thalassaemic patients compared with non-thalassaemic controls due to abnormal trace element metabolism in patients were reported [28,30]. Our study showed that in thalassemic

patients hypozincemia is common but there is no copper deficiency, Similar reports were provided by other researchers[11, 18,27]. Al-Samarrai et al attributed the cause of hypozincemia in thalassemic patients to hyperzincuria resulted from following hemolysis of red blood cells[18]. Hashemi Poor et al demonstrated that zinc concentration of hair in thalassemic patients (112.7±53.11 ppm) was lower than that in control group (149.6±72.21 ppm). They suggested that the etiology of zinc deficiency is malnutrition and inadequate zinc intake. They advise administration of zinc supplement[30]. On the other hand, Mehdizadeh et al have reported that mean serum zinc level was significantly higher in thalassemic group. They noted that zinc deficiency is rare in thalassemia[31]. 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[32]. Present study showed that 75% 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[23,24].

Serum copper level was found to be significantly increased ($p<0.005$) in our patients when compared with controls. Some studies showed that there was an increase in serum level of copper in patients experiencing thalassemia major[11–13, 18, 23, 28]. Al-Samarrai et al concluded that the etiology of hypercupremia is hemochromatosis, which is a principal complication of thalassemia. However, many reports [29,17, 19,22] revealed reduction in serum level of copper. Although study by Kassab-Chekir showed no change in copper concentration of serum[3]. 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]. Because there was no relationship between serum zinc and copper level and different variables such as duration of blood transfusion, desferrioxamine dose and age, so it is most likely that other risk factors unrelated to thalassemia disease such as nutritional status may be responsible for hypozincemia. There was a significant difference between serum ferritin level and the mean serum concentrations of zinc and copper in this study, Blood transfusion and increase copper absorption via the gastrointestinal tract could explain this finding. Our finding may be explained by the decreasing rate of glomerular filtration of zinc seen in chronic hemolysis and the disturbance in the metabolism of zinc and copper in thalassaemic patients due to the increasing serum copper and decrease serum zinc.

CONCLUSION:

Our data suggest that the increased level of iron and copper with zinc defeciency, which was noticed in all our thalassaemic patients is in concordance with other studies and confirm the unnecessary supplementation of zinc or other metal elements for thalassemic patients on regular blood transfusion

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مقارنة بين مستويات الخارصينِ، النحاس والحديد في الأطفالِ المصابين بالبيتا ثالاسيميا الرئيسي والأفراد الاصحّاء في مدينةِ النجف الاشرف .

تاريخ الاستلام : 29\12\2013 تاريخ القبول :30\3\2014

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الخلاصة :-

الثلاسيميا هي فقر الدم الوراثي الأكثر شيوعا في الإنسان. النوع الاكثر شيوعا من المرض هو ألفا و بيتا ثلاسيميا.ان بيتا ثلاسيميا الكبرى هي الشكل الأكثر شدة التي تتطلب نقل الدم المتكرر وحقن بعلاج ال ديفيروكسامين. تهدف الدراسة الحالية إلى تقييم مستويات كل من الحديدا،لنحاس والزنك في مصل الدم في مركز الثلاسيميا في مستشفى الزهراء في مدينة النجف شارك في هذه الدراسة أربعة وأربعون مريضا تراوحت اعمارهم(3-16 عاما) (20 ذكور و 24 إناث) كلهم يخضعون الى عمليات نقل الدم الدورية و الحقن بعلاج الديفيروكسامين (DFO) . شملت الدراسة خمسون شخص من الاصحاء من نفس العمر والجنس للمرضى (25 ذكور و 25 إناث) . وأظهرت النتائج أنخفاض مستويات الزنك معنويا ($P < 0.05$) في مرضى الثلاسيميا بيتا عند المقارنة مع الاصحاء ، بينما هناك زيادة معنوية في مستويات الحديد والنحاس ($P < 0.05$) عند مرضى البيتا ثلاسيميا الكبرى عند المقارنة مع مجموعة السيطرة. اوضحت الدراسة عدم وجود ارتباط كبير بين مستويات الزنك والنحاس في امصال الدم للمرضى مع التقدم في العمر ، ومدة نقل الدم ، ومستويات جرعة ديفيروكسامين، فقط وجد ان هناك علاقة ارتباطية بين مستويات الزنك والنحاس ومستوى االفيريتين في مرضى البيتا ثلاسيميا الكبرى.

الكلمات المفتاحية: الزنك، النحاس، الحديد، بيتا تلاسيميا الرئيسي.