

**Evaluation Zinc, Copper and Iron Concentrations in Children with Beta- Thalassemia Major in Diyala Province**

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**Abstract**

Some previous studies were inducted condition of a deficiency of zinc and its relation with a change in serum concentration of copper and iron in the thalassemic patients. The goal of our study was to evaluate zinc, copper, and iron serum level in children who have beta-thalassemia major. In this study, we took 52 cases all of them were children between one year to 15 years. Where 41 cases have beta thalassemia major and 11 cases are control group. The patients were covered by Al-Batol hospital and they have been evaluated for zinc, copper, and iron serum levels. The determination of serum for zinc and copper were achieved by atomic absorption spectrophotometer. Where serum iron was measured by cobas integra 400 plus. The study was done from August 2015, to June 2016. Serum zinc level was lower in thalassemia patients ( $49.90 \pm 38.13 \mu\text{g/d}$ ) than control group ( $65.00 \pm 12.03 \mu\text{g/dl}$ ). Comparing the level of copper in patients ( $101.57 \pm 37.03 \mu\text{g/dl}$ ) and controls ( $150.77 \pm 37.03 \mu\text{g/dl}$ ), we found the copper levels in patients was lower. The level of serum iron ( $32.81 \pm 9.24 \mu\text{mole/L}$ ) on beta thalassemia major, which was statistically higher in comparing to the controls cases ( $9.33 \pm 3.38 \mu\text{mole/L}$ ). Serum glucose level was higher in thalassemic patients  $5.10 \pm 0.08 \text{ mmole/L}$  than control group  $4.95 \pm 0.85$ . Thalassemic patients who had less than  $70 \mu\text{g/dl}$  of zinc concentration (hypozincemia) were (82.9%). Thalassemic patients, who had less than  $70 \mu\text{g/dl}$  copper concentration, were (17.07%). The correlation was not significant between zinc and copper of serum concentration and serum level of iron. There was no significant relation between serum zinc level of thalassemic patients with weight, glucose and number of blood

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transfusions ( $P=0.1$ ). However, there was a significant relation between serum zinc level of thalassemic patients with age and duration time of blood transfusion ( $P=0.04$ ). This study showed that thalassemic patients commonly have zinc deficiency. While, copper deficiency is found in seven cases. Additional valuation is recommended in this aspect.

**Keywords:** Beta-thalassemia; Zinc; Copper; Children; Iron

### تقدير تراكيز الزنك، النحاس والحديد في الأطفال المصابين بمرض بيتا ثلاسيميا الكبرى في محافظة

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### الخلاصة

اثبتت بعض الدراسات السابقة حدوث انخفاض لعنصر الزنك وعلاقته مع التغيرات التركيبية للنحاس والحديد في المصل في مرضى الثلاسيميا. كان الهدف من دراستنا تقييم مستوى الزنك، النحاس، والحديد في مصل في الأطفال المصابين بمرض بيتا ثلاسيميا. في هذه الدراسة، تم اخذ 52 حالة تتراوح اعمار هؤلاء الأطفال بين سنة واحدة إلى 15 سنة. تضمنت الدراسة 41 حالة مرضى مصابين ببيتا الثلاسيميا و 11 حالة هم مجموعة ضابطة. تم اخذ عينات الدم من المرضى في مستشفى البتول وقد تم حساب مستويات الزنك والنحاس، والحديد في مصل الدم. تم قياس تركيز الزنك، والنحاس باستخدام جهاز الامتصاص الذري بينما تم قياس تركيز الحديد باستخدام جهاز كوباس انتيغرا. اجريت الدراسة بالفترة مابين شهر اب 2015 الى شهر حزيران 2016. بينت الدراسة انخفاض مستوى الزنك في المرضى ( $5.95 \pm 49.90$ ) مقارنة مع تركيز الزنك في الاصحاء ( $65.00 \pm 12.03 \mu\text{g/dl}$ ). عند مقارنة مستوى النحاس في المرضى ( $101.57 \pm 37.03 \mu\text{g/dl}$ ) مع مستوى النحاس في الاصحاء ( $150.77 \pm 37.03 \mu\text{g/dl}$ ) وجدنا مستوى النحاس في المرضى كان اقل من الاصحاء. مستوى الحديد في المرضى ( $32.81 \pm 9.24 \text{ umole/L}$ ) اعلى معنويا من مستوى الحديد في الاصحاء ( $9.33 \pm 3.38 \text{ umole/L}$ ). لا يوجد ارتباط معنوي بين تراكيز الزنك والنحاس مع تركيز الحديد. النسبة المئوية لمرضى الثلاسيميا الذين يعانون من نقص بالزنك هي (82.9%) بينما الذين يعانون من نقص بالنحاس هي (17.07%) فقط. اثبتت الدراسة الحالية عدم وجود علاقة معنوية بين مستوى الزنك بالمصل مع الوزن، السكر، وعدد مرات نقل الدم (الاحتمالية=0.1). بينما هنالك علاقة معنوية بين مستوى الزنك بالمصل مع العمر و فترة نقل الدم عند (الاحتمالية=0.04). اكدت هذه الدراسة بأن المرضى المصابين بمرض الثلاسيميا عادة يعانون من نقص بعنصر الزنك.

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بينما هنالك فقط سبع حالات من المرضى يعانون نقص في عنصر النحاس لهذا نوصي بالجراء دراسة تشمل عدد اكبر من المرضى للتأكد من تراكيز هذه العناصر.

الكلمات المفتاحية: البيتا ثلاسيميا ، الزنك، النحاس، الاطفال ، الحديد

### Introduction

In human, Thalassemia is most common genetic anemia <sup>[1,2]</sup>. Initially, Cooley and Lee were described the disease <sup>[1,2]</sup>. Thalassemia gene is too widespread in regions of Mediterranean in comparing to the world. It is almost carried by 150 million people <sup>[3,4]</sup>. Beta and Alpha thalassemia are the more common disease types. Beta thalassemia causes reduction in the hemoglobin, iron-containing protein, production, it characterizes as blood disorder. Hemoglobin is responsible for carrying O<sub>2</sub> to body cells via red blood cell. As consequence of this type of thalassemia, Oxygen is lack in many part of the body because of the hemoglobin level is lower than normal. Also poverty of red blood cells (anemia), affected individuals, could lead to fatigue, weakness, pale skin, and more deliberative complications. Evolving abnormal blood clots hazard is increased at people that have bête thalassemia disease. Moreover, the treatment of patients would increase their life span, in the other hand, due to high contents of storage of iron in the body, various complications are observed, such as skeletal, metabolic, endocrine, and growth disorders <sup>[5,6]</sup>. In human development and growth, Zinc is played particular role. Since, it is very necessary for micronutrients in human and for more than 300 enzymes is acted as cofactor <sup>[7]</sup>. Similarly, copper considers an essential micronutrient with highest amount in brain, liver, kidneys, and heart. Also in many enzymes, it is important structural co-participant. It is acting like cofactor in most of enzymatic reactions including those of lysyl oxidase, cytochrome C oxidase, thyrosinase, and superoxide dismutase <sup>[4,8]</sup>. In addition, patients who have beta thalassemia major are suffered from zinc deficiency that can consider as one reasons of delay maturity in them that are reported <sup>[7,9,10]</sup>. In patients with thalassemia major a change in copper's serum level is indicated and reported. Kajanachumpol et al reported a higher concentration of copper while Shamshirsaz et al

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reported lower serum concentration of copper <sup>[9,11]</sup>. This study aims to evaluate the levels of zinc, copper and iron in the serum of Diyala province patients with beta thalassemia major.

### Methods

In this study, all cases were children between one year to 15 years old. The cases were classified in two groups of children, one of the group have beta thalassemia major (n=41) and the other one as controls (n=11). The patients were covered by Al-Batol hospital and they have been evaluated for zinc, copper, and iron serum levels. The study was done from August 2015, to June 2016. In this report, the cases older than 15 years were eliminated as well other hemoglobinopathies. History of disease, treatment as well anthropometric and demographic data has been recorded by measurement of laboratory, medical records, and physical examination. They used Sec a scale to measure the patient's weight without shoes and minimum clothes; the instruments precision rate is 100gr. The validity and reliability of instruments were checked on a regular basis. Because of the international standard of zinc, copper, and iron serum values in children. Tietz Textbook of Clinical Chemistry describes the normal ranges of serum copper value and was 70- 150 $\mu$ g/dl, also the normal ranges of serum zinc value and was 70- 120 $\mu$ g/dl <sup>[12]</sup>. The normal ranges of serum iron value was 5.8 – 34.5  $\mu$ mole/L. To determine the concentration serum of zinc, copper, and iron we use 5 ml blood samples. The samples were transferred into labeled tubes after that we centrifuged them at 2500 rpm. Clean tips were used to transfer the serum samples and kept at -20C prior to use. Then, we transferred the serum samples to the Research Laboratory in Chemistry Department at Diyala University in Diyala province. Both zinc and copper of serum were measured by Flame Atomic Absorption Spectrophotometer (AAS) technique using Aurrora Analyst 2003 Atomic. Glucose and iron were measured by Cobas Integra 400 Plus. The thalassemic patients were divided into 2 groups depended on the serum value of zinc and copper (70- 120 $\mu$ g/dl and 70-150 $\mu$ g/dl respectively). The variables such as weight, age, glucose... etc was compared in both groups. We documented and analyzed the data by t-test. *P*-value <0.05 was considered as significant.

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### Results

The study was conducted on 41 patients all of them have beta thalassemia major, 20 (48.7%) cases of them are males and 21 (51.2%) are females. We found serum zinc level was lower in thalassemia patients ( $49.90 \pm 38.13 \mu\text{g/dl}$ ) than control group ( $65.00 \pm 12.03 \mu\text{g/dl}$ ). Whereas, comparing the level of copper in patients ( $101.57 \pm 37.03 \mu\text{g/dl}$ ) and controls ( $150.77 \pm 37.03 \mu\text{g/dl}$ ), we found the copper levels in patients was lower. In addition, The level of serum iron ( $32.81 \pm 9.24 \text{ umole/L}$ ) on beta thalassemia major, which was statistically higher in comparing to the controls cases ( $9.33 \pm 3.38 \text{ umole/L}$ ). Serum glucose level was higher in thalassemic patients  $5.10 \pm 0.08 \text{ mmole/L}$  than control group  $4.95 \pm 0.85$ . The age of patients were between 12 and 180 months likewise the mean age was  $97.17 \pm 48.35$  months in thalassemic patients. The mean age in control group was  $97.12 \pm 48.20$  months. Moreover, the mean duration of blood transfusion was  $75.90 \pm 6.1$  months. The mean interval of blood transfusions was  $23.6 \pm 6.2$  days (Table1).

**Table 1: Biochemical data (mean  $\pm$  SD) in children with beta thalassemia major and control group**

Variable	Mean $\pm$ SD patients	Mean $\pm$ SD control group	P value
Cu ( $\mu\text{g/dl}$ )	$101.57 \pm 37.03$	$150.77 \pm 37.03$	$P < 0.05$
Zn ( $\mu\text{g/dl}$ )	$49.90 \pm 38.13$	$65.00 \pm 12.03$	$P < 0.05$
Fe (umole/L)	$32.81 \pm 9.24$	$9.33 \pm 3.38$	$P < 0.05$
Glucose (mmole/L)	$5.10 \pm 0.51$	$4.95 \pm 0.85$	$P < 0.05$
Age (mo)	$97.17 \pm 48.35$	$97.12 \pm 48.20$	$P > 0.05$
Duration of blood transfusions (per month)	$75.90 \pm 39.51$	-	-
Number of blood transfusions (per month)	$23.6 \pm 6.2$	-	-

The result show that (82.9) percent of patients had hypozincemia, (9.7) percent of patients had normal concentration and only (7.3) percent of patients showed concentration more than normal as shown in (Table2). There are (17.07) percent of patients showed concentration less than normal, (70.7) percent of patients had normal concentration and (12.19) percent of patients showed concentration more than normal as can be seen in (Table2).

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**Table2: Serum zinc and copper concentrations in beta thalassemic patients**

Trace Elements	Value	Number %
Serum Zinc	Less than normal (<70)	34(82.9)
	>70 Normal	4(9.7)
	>120 Up normal	3 (7.3)
	Total	41(100%)
Serum Copper	Less than normal (<70)	7(17.07)
	>70	29 (70.7)
	>150 Up normal	5(12.19)
	Total	41 (100%)

In our study cases, the correlation was not significant between zinc and copper of serum concentration and serum level of iron, as show in (Table 3).

**Table (3):The Correlations between serum iron level and serum concentrations of zinc and copper in children with beta thalassemia major**

Variable	Correlation Fe	
	r	p
Zinc	r	-0.272
	p	0.085
Copper	r	-0.236
	p	0.138

The variances equality of variable calculated, two or more groups are assessed by Levene's test which is an inferential statistic. Variance homogeneity might be measured by conducting test of Levene. In the event that the subsequent p-value of Levene's test is more than some significance level (typically 0.05),the got contrasts in test differences are probably going to have happened in view of random inspecting from a populace with equivalent changes. In this manner, the invalid speculation of equivalent changes is acknowledged (Table 4).

There was no significant relation between serum zinc level of thalassemic patients with weight, glucose and number of blood transfusions ( $P=0.1$ ) (Table 4). Also there was significant relation between serum zinc level of thalassemic patients with age and duration time of blood transfusion ( $P=0.04$ ) (Table 4).

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**Table4: The relationship between mean serum concentrations of zinc and different variables in children with beta thalassemia major**

Variable	Levene's Test		Zinc $\leq$ 70	Zinc $>$ 70	P Value
	F	Sig	Mean $\pm$ SD (34)	mean $\pm$ SD (7)	
Age	0.1	0.7	104.82 $\pm$ 44.53	60.00 $\pm$ 52.30	0.02
Weight	0.1	0.6	26.86 $\pm$ 11.48	20.85 $\pm$ 13.90	0.2
Fe	0.05	0.8	33.90 $\pm$ 9.08	27.51 $\pm$ 8.74	0.09
Glucose	0.08	0.7	5.10 $\pm$ 0.51	5.09 $\pm$ 0.59	0.9
Duration of blood transfusions (mo)	0.02	0.8	81.52 $\pm$ 37.57	48.57 $\pm$ 39.91	0.04
Number of blood transfusions (per month)	3.7	0.6	22.9 $\pm$ 6.2	27.1 $\pm$ 4.8	0.1

**Table5: The relationship between mean serum concentrations of Copper and different variables in children with beta thalassemia major**

Variable	Levene's Test		Copper $\leq$ 70	Copper $>$ 70	P Value
	F	Sig	Mean $\pm$ SD (7)	Mean $\pm$ SD (34)	
Age	1.7	0.1	41.40 $\pm$ 9.64	96.35 $\pm$ 50.52	0.8
Weight	0.02	0.8	24.85 $\pm$ 14.53	26.04 $\pm$ 11.60	0.8
Fe	0.9	0.3	20.07 $\pm$ 26.38	32.72 $\pm$ 9.69	0.8
Glucose	0.08	0.7	5.25 $\pm$ 0.46	5.06 $\pm$ 0.52	0.3
Duration of blood transfusions (mo)	0.4	0.5	75.00 $\pm$ 35.83	76.08 $\pm$ 40.72	0.9
Number of blood transfusions (per month)	1.2	.03	21.4 $\pm$ 6.2	24.1 $\pm$ 6.2	0.3

There was no significant relation between serum copper level of thalassemic patients with age, weight, glucose, duration time of blood transfusion, number of blood transfusions and iron level ( $P=0.8$ ) (Table 5).

### Discussion

The study showed that thalassemic patient's hypozincemia is common however there are only seven patients had copper deficiency in our study. The beta thalassemia disease is the major type and in order to continue the patients' lives repetitive chelation therapy and blood

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transfusions are needed. Even though the life span of patients has been improved to 4th and 5th decade by using new therapies, they are suffer from variety of complications like endocrinopathy, growth impairment, hypogonadism and others <sup>[1,2]</sup>. Even though there are well documented of iron accumulation role in presence of these complications, several reporters are emphasized the copper and zinc role that associate with such clinical problems <sup>[13-17]</sup>. Zinc is the most important mineral preceded after iron and considered like the critical micro-nutrients in human. Zinc works as the cofactor for over 300 enzymes. Some clinical disorders such as the growth impairment, hypogonadism, steoporosis, osteopenia, immunologic disorders, and repeated infections observe as the reason for zinc deficiency <sup>[7]</sup>.

A study done by Tabatabei et al showed zinc deficiency was appeared in 84.8% of thalassemic major patients. They demonstrated that lacking zinc of dietary intake of thalassemic major patients cause to zinc deficiency in these patients <sup>[18]</sup>. A study by Yazdiha et al reported that concentration of serum zinc in patients were less than the concentration of serum zinc in in control group, further there was statistically significant difference, was reported by Yazdiha et al. Also for thalassemic patients they recommended supplement of zinc <sup>[10]</sup>. In addition, other researchers provided similar reports <sup>[11,19-24]</sup>. Some researchers demonstrated that the serum concentration of zinc in control group was more than in thalassemic patients <sup>[11,19-24]</sup>. Similar reports was provided by Yazdiha et al <sup>[10]</sup>. Hemolysis of red blood cells caused elevation of serum zinc levels which lead to hypo zincemia in thalassemic patients that recognized by Al-Samarrai et al <sup>[21]</sup>. Hashemi Poor et al proved that concentration of serum zinc of hair control group was higher than that in thalassemic patients where, they recommended that the causes of hypo zincemia are undernourishment and insufficient zinc consumption. The research group recommends that management of zinc supplement <sup>[25]</sup>. They provided that the serum zinc levels in patients group was considerably higher <sup>[26]</sup>.

Reshadat et al results noted that high percentage (77%) of thalassemic patients have typical zinc concentration and the residues higher than typical. The group highlighted that these patients' medical treatment is inappropriate, hence the value of zinc management ought to be more evaluated <sup>[27]</sup>.



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In comparing to previous study, Kosarian et al reports stated that major thalassemic patients are not influenced by zinc deficiency, because they found the serum level of zinc in control group and major thalassemic patients were not beyond the typical limits <sup>[28]</sup>. A study found that hypozincemia in thalassemic children was thirty four percent. These patients might be suffer from zinc deficiency which are correlated to irregularity in urinary absorption of zinc, disturbance in zinc metabolism, urinary zinc secretion, inadequate zinc amount in daily meals, abnormality, and higher level of zinc excretion in sweat <sup>[1-4]</sup>.

Because of there is no association between serum level of zinc and numerous variables such as weight, glucose, number of blood transfusions. Therefore, hypozincemia could be caused by other risk factor like nutritional status which is not related to thalassemia disease.

There was significant relation between serum zinc level of thalassemic patients with age and duration time of blood transfusion. Zinc ratio in human body is 2-3 g, and some organs containing esteemed zinc concentrations include liver and kidney <sup>[29]</sup>. Since repeated blood transfusions have dangers and side effects like transfusion-transmitted infections such as hepatitis C virus (with high risk of developing chronic hepatitis, liver cirrhosis and hepatocellular carcinoma), whose risks increases with the age of child and number of red cell transfusions done. Consequently, it is affect zinc concentration in human body.

Also, Copper is fundamental trace element of human body and mostly devoted to albumin and ceruloplasmin. More than 30 enzymes depend on copper as the cofactor therefor, many signs of copper deficiency and poisonousness are related to abnormalities in these enzymes <sup>[4,8]</sup>. There are studies presented that increasing in copper serum level in patients, whom have thalassemia major, was found <sup>[11-14,22,24,30]</sup>. A study of Al-Samarrai et al reported hypercupremia etiology is hemochromatosis that is a major complication of thalassemia <sup>[21]</sup>. Though, studies by Naser<sup>[20]</sup>, Tabatabaei <sup>[18]</sup>, Bekheirnia <sup>[31]</sup>, and Eshghi <sup>[23]</sup> exposed decreasing in serumcopper level. Although report of Kassab-Chekir indicated there is no variation in serum concentration of copper <sup>[21]</sup>. The copper concentration of serum in thalassemia major patients is be subject to several factors such as copper uptake by intestine, ratio of copper to zinc, kidney function, iron accumulation, copper amount consumption in daily diet, and Desferal administration <sup>[11,14]</sup>.

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The results showed seven of our cases (41 patients) had a copper deficiency and five of our cases had copper concentration more than normal, which inducted that the factors, influence level of copper, are uncontrolled. Furthermore, there is no association between serum level of copper and numerous variables such as weight, glucose, number of blood transfusions. Also, copper deficiency could be caused by other risk factor such as kidney function which is not associated to thalassemia disease.

### Conclusion

This study showed that thalassemic patients commonly have zinc deficiency. While, copper deficiency is found in seven cases only. Additional valuation is recommended in this aspect. The correlation was not significant between zinc and copper of serum concentration and serum level of iron.

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