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Assessment of Serum Zinc Level in Children with Thalassemia Major Receiving Oral Chelation and Their Sibling in AL-Najaf City

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Abstract: ***Background: Thalassemia is commonest hereditary anemia, Iraq is among countries with highest prevalence of major thalassemia, thalassemia patients have poor growth and delayed maturation mainly due to iron overload but zinc deficiency also has been suggested as a contributing factor. Aim of the study: To determine serum zinc level of patients with thalassemia and their healthy sibling and to determine whether the possible deficiency is influencing by the disease itself or by other factors. Patients and Methods: A case-control study was carried out from February 2016 to august 2016 in Al-Zahraa teaching hospital for maternity and children in Al-Najaf province .the study included 80 patients with thalassemia their ages range from 5-15 years. Control group was 50 of apparently healthy children without acute or chronic diseases, their ages range from 5-15 years , control group selected and matched with disease group regarding sex & age. For each patient & control group 3ml of blood was taken at morning , serum zinc measured by spectrophotometer and the data analysis don by SPSS version 22, 2014. Results: mean serum zinc levels were 56.2±16.1,59.5±17.7& 60±14.6 µg/dL in Transfusion dependent, non-dependent and normal control respectively with no statistical differences, also the study show no significant relationship between serum zinc level and different variables such as gender, age, ferritin level &duration of oral chelation therapy (p>0.05) while there is significant relationship between serum zinc level and body mass index(p<0.05). Conclusion: Zinc deficiency prevalent in thalassemia & non thalassemia children in Al-Najaf province, suggesting that serum Zn levels are possibly more influenced by familial and environmental factors rather than by thalassemia per se or its treatment.***

Keywords: β-thalassemia, zinc deficiency, oral chelation therapy, Najaf, Iraq

1. Introduction

Thalassemia is the most common hereditary anemia [1, 2]. This severe hereditary anemia needs blood transfusion for life. According to this form of treatment, different problems like metabolic, endocrine and growth abnormalities would occur [3-5]. Chronic blood transfusion in thalassemia major or other hemolytic disorders such as Sickle cell anemia may decrease chronic hemolysis and change the micronutrient status [6-8]. Zinc is a trace element needs for synthesis of many other properties like cholesterol, fat and more than 300 enzymes and immune and antioxidant system

[9, 10]. Zinc has an important role in red blood cell survival and zinc deficiency leads to membrane fragility [11]. Many nutrient products contain zinc. High levels of zinc found in oysters, red meat, poultry, beans, nuts, some seafood, whole grains, fortified breakfast cereals, and dairy products, while Vegetables, fruits, tea, coffee, rice and bread have low zinc levels[12]. Zinc affects growth in children. It is known that adequate zinc levels in the body are important for maintaining agood levels of growth hormone and insulin-like growth factor in the body [13]. Decrease of zinc levels will ultimately lead to growth hormone deficiency. Zinc supplement is given to children on growth hormone replacement therapy. Although, zinc is important for nucleic acid synthesis, cell division, and metabolism of lipids, proteins and carbohydrates. It is also essential in bone homeostasis and bone growth as well as in the maintenance of connective tissues. Decreased Zn may affect the growth and immune functions [13,14].

Zn is important for the integrity of the immune system, although its role and mechanism of action are not so clear [15, 16-18]. Zn deficiency affects the adaptive immune system and results in thymus atrophy, lymphopenia, and impaired lymphocyte function [16, 19, 20].Zinc deficiency is common in children of developing countries where food is mainly contains vegetable and rarely includes animal products. Zinc is easily absorbed with animal proteins, while excess plant meals lead to decreased zinc absorption due to its binding to phytates[21,22].In such countries, Zn deficiency leads to growth retardation, hypogonadism, and increased mortality and morbidly from infection-related diarrhea and pneumonia because of compromised immune function [16,21].

Zinc deficiency in thalassemic patient is due to various causes which are either attributable to iron chelation,limited diet, increased urinary zinc excretion and ongoing hemolysis [23, 24, 25, 26]

In the present study, we aimed to assess serum Zn levels in patients with thalassemia and their siblings in a lower middle income country, namely, Iraq, to determine whether Zn deficiency is present and, if so, if it is related to the disease per se, use of chelation or to nutritional factors.

2. Patients and Methods

Subjects

A case-control study was carried out from February 2016 to august 2016 in Al-Zahraa teaching hospital for maternity and children in Al-Najaf province .the study included 80 (46male,34female)patients with thalassemia their ages range from 5-15 years .

Inclusion criteria: age 5 -15 years, documented thalassemia (with hemoglobin electrophoresis) all on regular oral chelation therapy, normal kidney and liver function tests.

Exclusion criteria: liver disease, kidney disease, gastrointestinal disease, patients with recent infections,

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fever, diarrhea, specific diet habit such as vegetable regimen, and consumption of zinc and minerals.
Details regarding age, sex, residency, age of onset and duration of disease, the frequency of transfusion, , history of chronic disease, and drug history were taken.

Control group was 50 (25male, 25female) of apparently healthy children without acute or chronic diseases, their ages range from 5-15 years with mean of 8.5 ±2.7. selected and matched with disease group regarding sex & age.

Method:
After overnight fasting, blood samples of 3 ml were collected. All blood samples were centrifuged after spontaneous coagulation and then stored at -20ºC. Zinc level was measured using atomic absorption spectrometry (Jena, Germany)with special kit for colorimetric determination of zinc in serum. A cut-off value was 70-115 µg/dl according to kit instructions. Samples below 70 µg/dl was regarded as hypozincemia .

The following data were obtained from the patients' clinical file records: blood transfusion history, last ferritin measurement, onset of chelation therapy and type of chelation used, and infection profile. In addition to serum Zn levels, anthropometric measures such as height, weight, and body mass index (BMI) (BMI = weight (kg)/height2 (m2) were obtained).

Statistical analysis
Statistical analysis was done by using the statistical package for social sciences (SPSS) version 22, 2014. Statistical analysis was performed using t-test, chi-square tests and Persons correlation (r).P-value set at ≤ 0.05 is be considered as significant difference or association between study variables and no significant difference when P >0.05.

3. Result

The study included 80 children suffering from Hb E-b thalassemia and 50 children are healthy age and sex matched controls who are not suffering from thalassemia.

Mean age in this study was 8.9 with standard deviation 3.1 in patients with HbE – â thalassemia and those in control group mean age was 8.5with SD-2.7.

Total 71 children were male while 59 children were female in this study. In Hb E- âthalassemia group 49(57.5%) cases were male while 34 (42.5%) cases were female but in control group it was 25(50%) and 25(50%) respectively as shown in tabl(1).

In this study 60(75%) of patient with thalassemia and 33(66%) in control have low sr. Zn level as shown in table(2).

In this study out of 46 male 31(51.7%) and out of 34 female 29(48.3%) have low sr. Zn level as shown in table(3)

In this study out of 60 patient who had low sr. Zn level the mean age was9.63 and SD 3.3, mean of duration of chelation was 3.53 and SD 1.4, the mean of sr. ferritin 3021.57 and SD 2165.9, mean of BMI was 16.58 and SD 2.3 as shown in table(4).

In this study there is weak positive correlation between zinc level and age of patient
(P value =0.06)as shown in figure(1).

There is weak negative correlation between zinc level and ferritin (P value= 0.7) as shown in figure(2)

Not significant weak positive correlation between zinc state and chelation period (P value=0.6) as shown in figure(3).
In this study there is significant positive correlation between BMI level and zinc level (P value=0.0001*) as shown in figure(4).

Table 1: Descriptive statistics of different variables in studied groups

		Cases	Control	Total	P
		N=80 No. (%)	N=50 No. (%)		
Gender	Female	34(42.5%)	25(50%)	59	0.4
	Male	46(57.5%)	25(50%)	71	
Age group/yr.	5-9	38(47.5%)	32(64.0%)	70	0.066
	9-15	42(52.5%)	18(36.0%)	60	
Mean ±SD		8.9±3.1	8.5±2.7		0.8
BMI	5th-84th Percentile*	63(78.8%)	40(80.0%)	103	0.1
	85th-95th Percentile**	5(6.2%)	8(16.0%)	13	
	Below 5th Percentile ***	12(15.0%)	2(4.0%)	14	
Mean ±SD		16.9±2.2	16.95±2.3		0.2
S.ferritin	Normal (< 500ng/mL)	5	-		
	high (≥ 500ng/mL)	75	-		
Mean ±SD		2995.9 ± 2219	-		
Duration of oral chelation mean ±SD		3.5±1.4			

* = normal BMI, ** = over weight , *** = underweight

Table 2: Comparison of zinc levels in cases & controls

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		Group		Total	P, OR(95% CI)
		cases N=80	control N=50		
Zinc	normal 70-115 µg/dL	20(25%)	17(34%)	37(28.5%)	0.3, 0.6(0.3- 1.4)
	low (less than 70µg/dL	60(75%)	33(66%)	93(71.5%)	
	Total	80(100%)	50(100%)	100(100)	

Table 3: Association between gender and zinc level in patients with thalassemia

		Gender		Total	P, OR(95% CI)
		Female N=34	Male N=46		
Zinc	normal 70-115 µg/dL	5 (25%)	15 (75%)	20(100)	0.7, 0.4(0.1- 1.1)
	low (less than 70µg/dL	29 (48.3%)	31 (51.7%)	60 (100)	
	Total	34 (42.5%)	46 (57.5%)	80(100)	

Table 4: The relationship between mean serum concentrations of zinc and different variables in children with beta thalassemia major

Variable	Normal 70-115 µg/dL N=20 Mean±SD	Low (less than 70µg/dl N= 60 Mean±SD	P
Age	11.15±3.8	9.63±3.3	0.09
Duration of chelation	3.35±1.4	3.58±1.4	0.5
Last.S.Frritin in ng/mL	2919.15±2428.6	3021.57±2165.9	0.9
BMI	18.10±2.8	16.58±2.3	0.02*

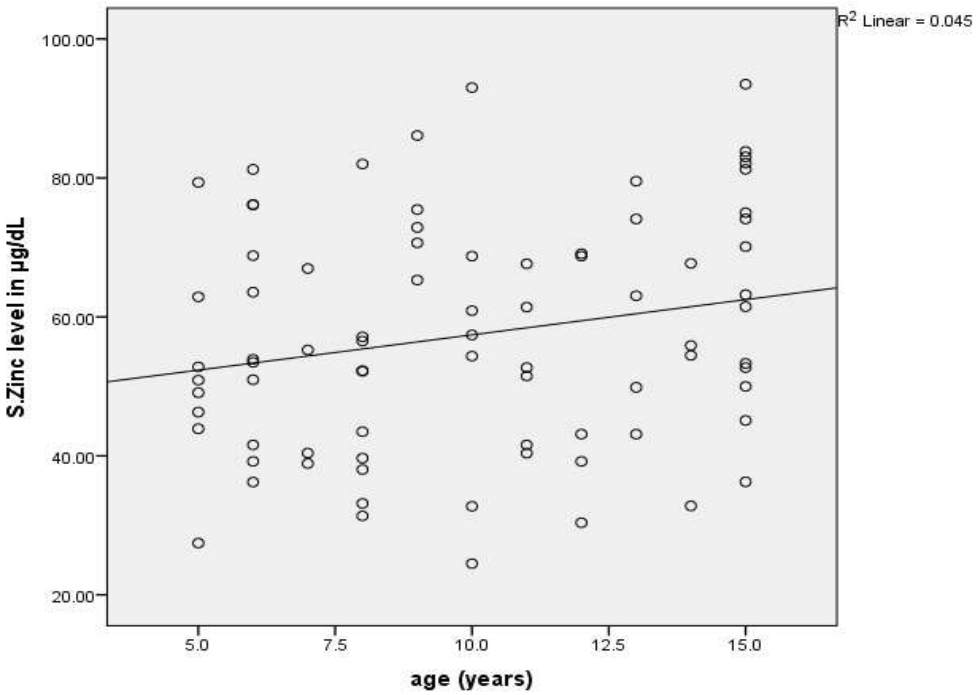

Figure 1: Not significant weak positive correlation between zinc level and age of patient (P value =0.06)

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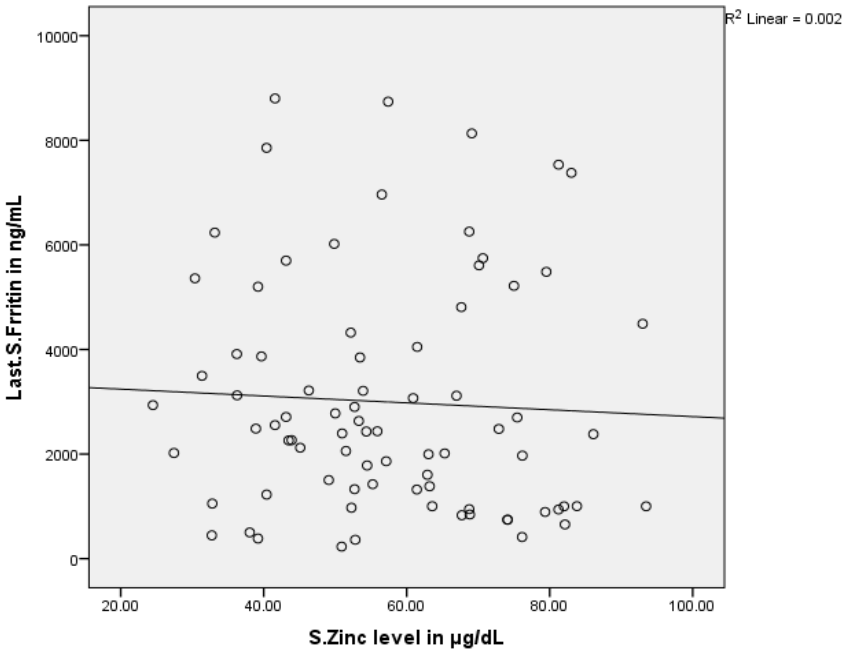

Figure 2: Not significant weak negative correlation between zinc level and ferritin (P value= 0.7)

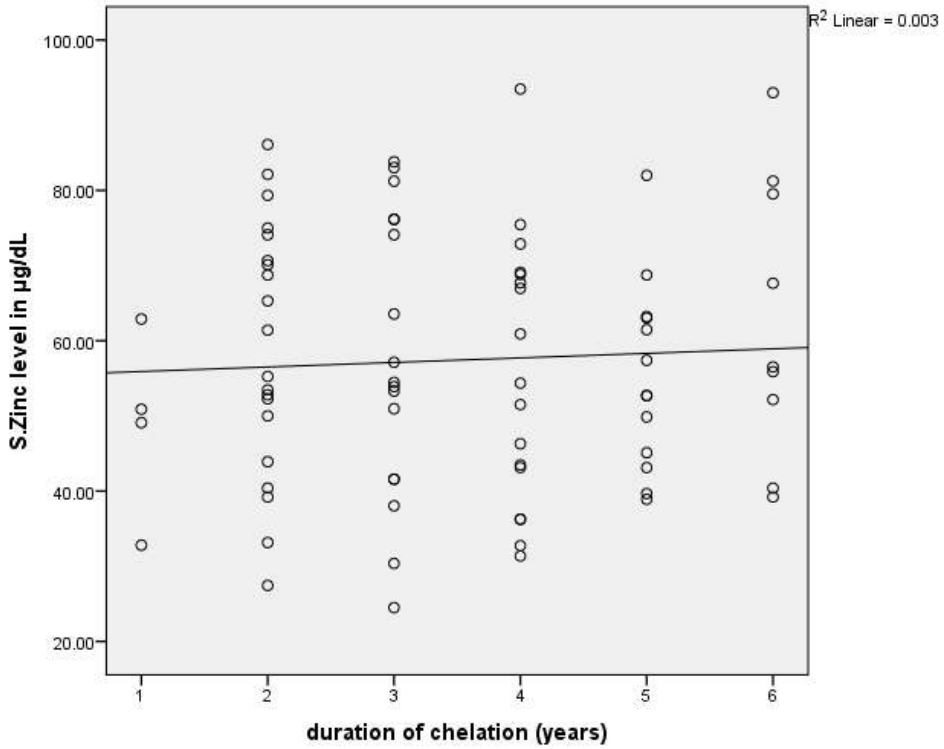

Figure 3: Not significant weak positive correlation between zinc state and chelation period (P value=0.6)

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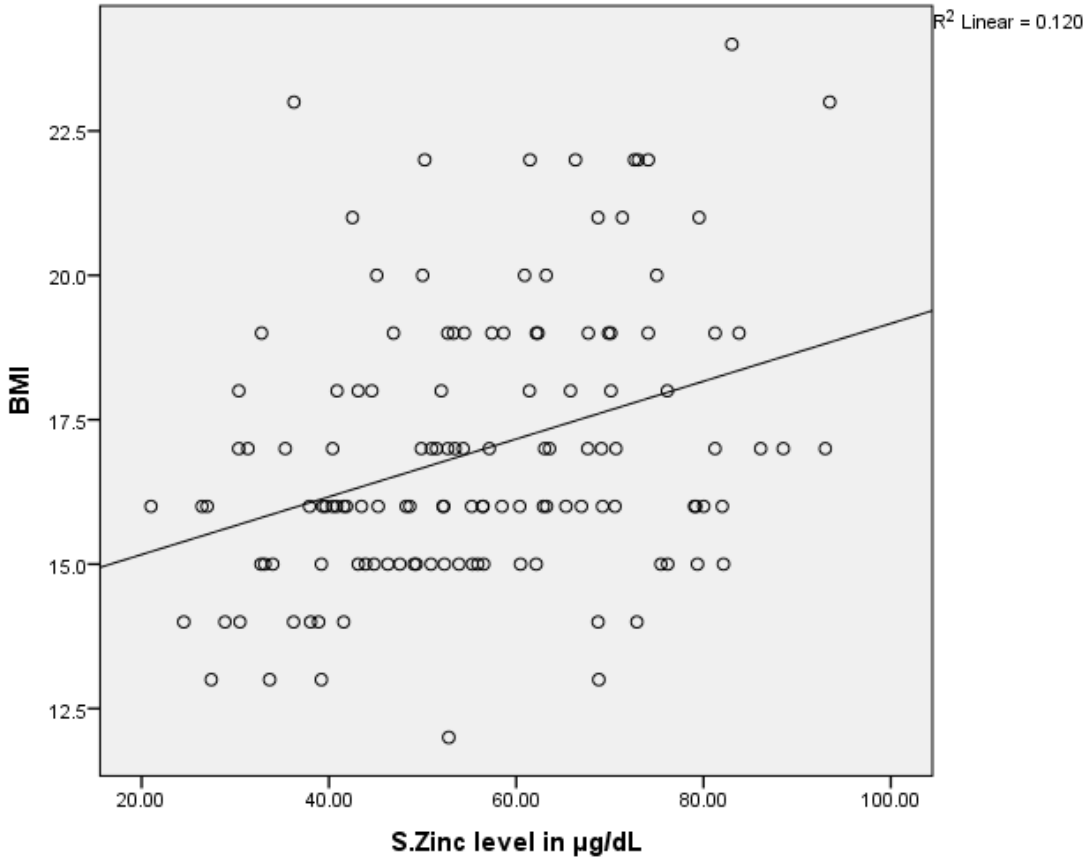

Figure 4: Significant positive correlation between BMI level and zinc level (P value=0.0001*)

4. Discussion

Zinc is an essential element for growth and immunity. In this study we aimed to compare serum Zn levels between thalassemia patients and their healthy siblings as to assess whether a possible deficiency is influenced by the disease itself or by nutritional and familial/environmental causes.

The present study assesses the status of serum zinc in thalassemic children on oral iron chelation.

This comparative study on 80 cases of thalassemia and 50 healthy controls, to be enrolled in this study, every patient and control volunteer must meet the inclusion & exclusion criteria of the study.

The main demographic, anthropometric and other relevant features of both thalassemic and control groups were comparable and there were no significant differences in factors such as age, sex & BMI (table 1).

The current study did not find any significant relation between serum zinc status in thalassemic patients and control group, because 33(66%) of control group had zinc deficiency as compared to 60(75%) of patient with thalassemia. With respect to reference cut-off point of serum zinc level (70 µg/dl) (table 2).

We expected 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 [27] but 66% of low zinc level in normal population indicates a health problem in our province. We found that the reason of zinc deficiency was inadequate zinc consumption which could be related to a high prevalence of insufficiency of this mineral in Al_Najaf city people.

In a study done in the same center in 2012 on patient with combined oral and injectable chelation drugs (Khadem, 2013) researcher found that about 49% of thalassemia patients & 18% of control suffer from Zn deficiency. This may contributed to difference in sample collection and use of oral chelation drugs only[28] .

Al Samarrai et al. study shows the zinc deficiency among tthalassemic and related it to hyperzincuria[29] Egyptcianstudy by Nasr et al shows that in a series of 64 patients, the mean zinc level was significantly lower (12.4±5.4µg/dl) in patients versus the control group (95.1±10.3µg/dl).[30]

Bekheirnia et al study in Tehran thalassemia center found 84.8% of thalassemiac patients to be zinc deficient was approximately near to our study[31] .

However, Moafi et al reported the prevalence of Zinc deficiency in TM patients as 10%, which was very lower as compared to our study[32].

Other researchers like Donma in Turkey and Mehdizadeh et al interestingly, found that the mean serum zinc level was significantly high in thalassemia group. These studies

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indicated that zinc deficiency in thalassemia patients who were on regular blood transfusion was rare and they showed that routine zinc supplementation is not necessary for most of TM patients[33,34]

The current findings are comparable with some researches and completely opposite to some studies, The different results may be related to sample size of each study(range from 40-333), differences in inclusions criteria, nutritional status of studied groups ,type of chelation therapy (as some of studied group was on injectable drug, other on oral or combined types), frequency, regularity & duration of transfusions.

The current study revealed no significant relationship between serum zinc level and different variables such as gender, age, ferritin level **&**duration of oral chelation therapy (table 4).

These results going with Mahyaretal, 2010 in Malaysia who reported that other risk factors unrelated to thalassemia disease such as nutritional status may be responsible for hypozincemia[35].

It appears that elevated ferritin levels are inversely related to Zn levels so that as ferritin increases, Zn decreases. However, in the current study, the correlation was not statically significant (p=0.9) and might be explained by inadequacy of clinical care and proper management affecting independently both ferritin and nutritional Zn levels.

In the present study, oral chelation therapy represented by Deferasirox (Exjade)® did not seem to affect zinc levels, this agree with a study by El Missiryetal(2014),although it have been reported that Deferoxamine and deferiprone chelate and eliminate zinc into urine, while for deferasirox, which has a lower affinity for divalent zinc, this seems not to be the case [36,37,38]

Also the study revealed that BMI significantly correlated with zinc level(0.02) this agree with a study by Kyriakou and Skordis (2009), as the authors proposed that Zn deficiency could be a concomitant factor for growth failure among patients with thalassemia [39] and this result did not agree with El Missiry etal,2014[38] and they explain their non-significant finding by the presence of other concomitant variables such as chronic anemia, iron overload-related endocrine problems, and impaired bone growth which play an important role [40].

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