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Original Article

Relationship between serum ferritin and zinc levels in pediatric thalassemia major patients

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Abstract

Background In thalassemia patients, reduced zinc absorption results from increased serum iron due to repeated blood transfusions, increased iron absorption due to ineffective erythropoiesis, and competitive inhibition between iron and zinc in binding to transferrin, a means of transporting both types of minerals in the blood. Few studies have been done to examine zinc levels in thalassemia patients and its relationship with ferritin.

Objective To compare serum zinc in thalassemia patients and healthy controls and to assess for a possible correlation between serum ferritin and zinc in thalassemia patients.

Methods This cross-sectional study in 68 subjects was done from October 2016 to August 2017. Serum ferritin measured by chemiluminescence immunoassay and serum zinc by inductively coupled plasma mass spectrometry (ICP-MS). Wilcoxon test was used to analyze for differences between serum zinc in thalassemia patients and controls. Spearman's correlation test was used to analyze for a possible correlation between ferritin and serum zinc in thalassemia patients.

Results There were 34 patients with thalassemia and 34 healthy control subjects. The median serum zinc was 119.34 μg/dL (IQR=71.27) in the thalassemia group and 120.08 μg/dL (IQR=26.28) in the control group (P=0.36). There was no significant correlation between serum ferritin and zinc in thalassemica children (r=-0.023; P=0.895).

Conclusion There is no difference in serum zinc levels between thalassemic children and healthy controls. There is no correlation between serum ferritin and zinc in thalassemica children. **[Paediatr Indones. 2019;59:144-9; doi: http://dx.doi.org/10.14238/pi59.3.2019.144-9]**.

Keywords: *HIV; thalassemia; ferritin; zinc*

Thalassemia is an inherited, autosomal recessive blood disorder characterized by abnormal hemoglobin synthesis that causes red blood cells to be easily damaged and fragile.[1] The main treatment for thalassemia is blood transfusion, in order to maintain hemoglobin levels above 10 g/dL.[2] Complications in thalassemia generally occur due to the disease itself (chronic anemia) and the main therapy, blood transfusion. Repeated blood transfusions cause iron accumulation in the tissues which can be aggravated by increased iron absorption due to ineffective erythropoiesis.[3,4]

Serum ferritin is used to monitor iron levels in the body. High levels of iron in children cause oxidative trauma and tissue siderosis. Complications, such as diabetes, liver cirrhosis, heart failure, hypothyroidism, short stature, and hypogonadism, often occur. In addition, osteoporosis, thromboembolism, zinc deficiency, and other complications can occur in patients with thalassemia.[5-7]

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Zinc is an important micronutrient found in almost every cell in the body. Zinc regulates enzyme systems that affect cell division and proliferation, wound healing, DNA synthesis, and maintaining normal structures and/or functions of several enzymes. Zinc is also very important for growth, puberty, and the immune system.[8,9] Several studies have been conducted on zinc deficiency in thalassemia major patients.[10-14] Further studies are needed to determine factors associated with low serum zinc levels and their relationship to serum ferritin levels of in such patients, hence, we aimed to evaluate serum zinc levels and its relationship to serum ferritin in children with thalassemia major treated at Dr. M. Djamil Hospital, Padang, West Sumatera.

Methods

This cross-sectional study was conducted from October 2016 to August 2017. Subjects were children in Dr. M. Djamil Hospital, Padang, West Sumatera, who fulfilled the inclusion criteria, and consisted of 34 thalassemia patients and 34 healthy children as controls. The inclusion criteria were thalassemia patients who were routinely transfused and whose parents agreed to take part in the study. The control group consisted of healthy children that had been adjusted for age and sex with the thalassemia patients.

Serum ferritin measured by chemiluminescence immunoassay and serum zinc by inductively coupled plasma mass spectrometry (ICP-MS). Data analysis and processing was done using *SPSS version 21* software. Wilcoxon test was used to analyze for differences between serum zinc in thalassemia patients and controls. Spearman's correlation test was used to analyze for a possible correlation between ferritin and serum zinc in thalassemia patients.

Study protocols and consent forms were approved by the Medical and Health Research Ethics Committee of Universitas Andalas Medical School/ Dr. M. Djamil Hospital.

Results

The 68 subjects, 34 thalassemic and 34 healthy children, categorized by age, namely, ≤10 years and >10 years. Most subjects were aged ≤ 10 years (20 children in each group, 58.8%). There were 10 children (29.4%) with undernourished nutritional status in the thalassemia group and 8 (23.5%) in the control group. No subjects had malnutrition. The highest incidence of stunting was 20 children (58.8%) in the thalassemia group, while the control group had 6 children (17.6%) with stunting. The characteristics of study subjects are shown in **Table 1**.

As shown in **Table 2,** the median zinc level in the thalassemia group was 119.34 μg/dL, whereas that in the control group was 120.08 μg/dL. Wilcoxon signed rank test revealed no significant difference in zinc levels between groups (P=0.36).

Statistical analysis of ferritin and serum zinc levels in thalassemia patients was tested done with Spearman's correlation test. Ferritin and serum zinc was not significantly correlated in thalassemia patients, as shown in F**igure 1**.

Table 1. Characteristics of study subjects

	Thalassemia group (n=34)	Control group (n=34)
Sex, n		
Male	18	20
Female	16	14
Age, n		
≤ 10 years	24	20
> 10 years	10	14
Nutritional status, n		
Well-nourished	24	21
Undernourished	10	8
Overweight	0	1
Obese	0	4
Stunting, n	20	6

Table 2. Serum zinc levels in the thalassemia and control groups

Groups	Zinc level			
	n	Median	IQR (range)	P# value
Thalassemia	34	119.34	71.27 (87.42-330.85)	0.36
Control	34	120.08	34 (26.28-91.26)	

Serum zinc units=μg/dL; #Wilcoxon signed ranks test

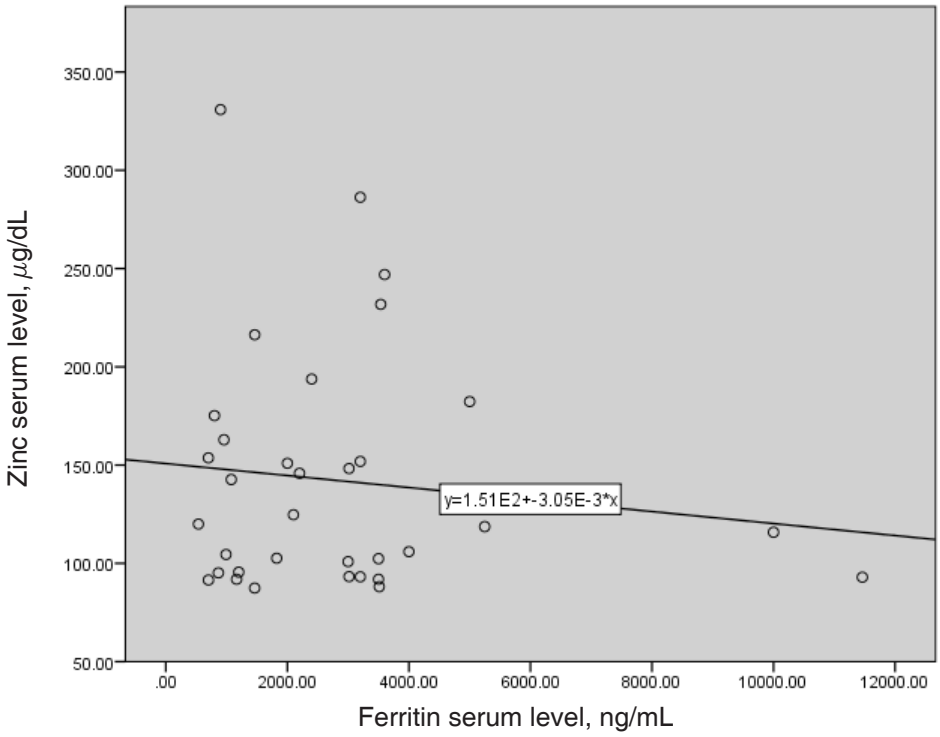

Figure 1. Correlation between ferritin and serum

Discussion

The two subject groups were categorized by age, either ≤ 10 years or > 10 years. The growth pattern in children with thalassemia who receive routine blood transfusions to maintain hemoglobin levels of more than 9 g/dL is relatively normal until the age of 9 to 10 years. Subsequently, regular transfusions cause iron overload, which triggers tissue damage, due to accumulation of free radicals in the organs. Thus, the speed of growth begins to decline, causing short stature and growth failure.[15,16]

There were 26 children with stunting, 20 in the thalassemia group and 6 in the control group. Growth disorders are quite common complications in children with thalassemia major. Tissue hypoxia due to chronic anemia, micronutrient deficiency, inadequate blood transfusion, iron buildup in endocrine organs, and hepatosplenomegaly cause a decrease in appetite so that food intake is reduced, resulting in nutritional disorders and failure to thrive in thalassemia patients.[17] Side effects from iron chelation therapy are also causes of growth disorders in patients with major thalassemia.15 The percentage of patients with stunting in our study was associated with the incidence of iron overload, in which 95% of stunting occurred in patients with ferritin levels >1,000 ng/mL.

Several studies have linked growth disorders in thalassemia patients with zinc deficiency. Arcasoy et al. showed that zinc deficiency is one of the factors responsible for delayed growth in thalassemia patients.[18] However, Mehdizadeh *et al.*,[19] Arijanti *et al.*,[20] and Eshghi *et al.*,[21] found no significant relationship between zinc levels and short stature. Faranoush et al. compared thalassemia patients who received zinc supplementation at a dose of 60 mg/day for 18 months, to thalassemia patients who did not get zinc. They showed that zinc supplementation was only useful in patients with zinc deficiency, otherwise zinc prophylaxis had no effect on growth.[22]

In several previous studies, serum zinc deficiency in thalassemia patients was associated with the incidence of chronic hemolysis, hyperzincuria, low intake of zinc in food, high iron content, and iron chelation. Arijanti et al. found that all subjects had zinc deficiency.[20] Arcasoy et al. noted a decrease

in zinc levels in plasma, erythrocytes, and hair, and increased zinc excretion in urine of thalassemia patients.[18] Hess *et al.* in Iran found that in 40 pediatric thalassemia subjects, more than 65% of patients with hypozincemia had zinc concentrations below 70 μg/dL.[23] Nidumuru *et al.* compared serum zinc levels in 35 thalassemia patients and to 35 healthy controls and reported that 65% of thalassemia patients had zinc deficiency.[12]

In our study, no subjects had zinc deficiency, nor did we find a significant difference in zinc levels between groups (P=0.36). In agreeement with this finding, Morshed et al. noted that serum zinc levels in thalassemia patients were within normal limits, so zinc supplementation was not needed.[24] Similarly, Kwan et al. reported that only 3 of 68 patients with thalassemia had zinc deficiency.[25]

We found higher interquartile range in thalassemia patients than in the control group, indicating more varied zinc levels in patients with thalassemia than the control group. Varied zinc levels may be due to variations in the age of subjects, the number of transfusions, and iron chelation therapy, or due to problems with anorexia, nutritional status, psychological problems, and different metabolic or endocrine complications. The highest zinc content was found in one thalassemia patient with 330.85 μg/dL. The patient at the time of the study was 3 years and 4 months old, with good nutritional and growth status, and 900 μg/dL ferritin level. This patient was routinely transfused every 4 weeks and never received iron chelation therapy, which may be a factor causing high zinc levels. High zinc levels in the thalassemia group compared to the control group were also reported in previous studies, possibly due to routine administration of blood transfusions, impaired zinc metabolism that occurs in patients with thalassemia, and a decrease in glomerular filtration rate.[26,27] A Tehran study examined zinc status in 64 people with beta thalassemia major compared to 64 healthy controls and obtained a significantly higher mean zinc level in thalassemia patients compared with the control group. They concluded that regular blood transfusions from healthy donors can prevent zinc deficiency.[19] A previous study in Jordan found a significant increase in zinc levels in the thalassemia group compared to the control group, due to a decrease in glomerular filtration rate of zinc and metabolic disorders of zinc that occur in thalassemia patients.[27]

Zinc concentration is higher in red blood cells. Patients who are dependent on transfusions have a higher serum zinc level than healthy controls. Kajanachumpol *et al.* reported an increase in erythrocyte zinc levels in thalassemia patients compared to healthy controls. The mechanism of increasing erythrocyte zinc is still unclear, but it is likely to be an effect of impaired zinc metabolism in the body which causes failure of zinc utilization in tissues of thalassemia patients.[28] The high serum zinc level in thalassemia patients is also associated with the possibility of liver parenchymal damage caused by hemosiderosis or a condition of decreased zinc glomerular filtration rate that occurs in chronic hemolysis.[19,27] The liver is a storage organ for zinc. Iron overload increases oxygen free radicals that induce peroxidative damage, increasing serum zinc from damaged hepatocytes. It has been hypothesized that variation in serum zinc level may be caused by endogenous leukocyte mediators that mobilize zinc from the liver and other tissues to the serum.[29] Metabolic zinc disorders are also a possible reason for high zinc levels in thalassemia patients.[27]

In patients with thalassemia, increased iron levels may be caused by recurrent blood transfusions and increased absorption due to ineffective erythropoesis.[14] Increased iron can inhibit the absorption of zinc in the gastrointestinal tract. There is a competitive inhibition between iron and zinc in binding to transferrin in the blood, while the administration of iron chelation in thalassemia patients would also chelate other important minerals including zinc.[30] Previous studies by Arijanty et al. and Nima et al. found that ferritin levels had a significant negative correlation with plasma zinc levels.[20,31] Similar results were also reported by Mahyar *et al.* in 2010 and Missiry *et al.* in 2014.[32,33] We noted a weak negative correlation between serum ferritin and zinc levels in thalassemia patients but it was not significant.

This study had several limitations, such as the small sample size. We also did not screen for a number of other clinical conditions that could bias the results of the study. The mechanism of increased zinc levels in thalassemia patients remains unclear and debatable. Further studies are necessary to determine factors that cause increased serum zinc levels in patients

with thalassemia.

In conclusion, there is no difference in serum zinc levels of pediatric thalassemia patients compared to healthy controls. In thalassemia patients, there is no correlation between ferritin levels and serum zinc levels.

Conflict of Interest

None declared.

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