



Zinc Status in Beta-Thalassemia Major

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Abstract

BACKGROUND: Zinc is one of the most important minerals incorporated in the enzymes of the human body. Zinc may be deficient in patients with the β -thalassemia major with possible adverse outcomes.

AIM: The purpose of this study was to assess the serum zinc status in β -thalassemia major patients in Duhok city.

PATIENTS, MATERIAL, AND METHODS: In this case-control study, 70 children with β -thalassemia major (2–12 years) of both genders were enrolled and were matched with 70 apparently healthy children for age and sex. A venous blood sample was obtained from each child for the measurement of serum zinc and serum ferritin levels at Jin Center in Duhok City between January 1 and June 30, 2017.

RESULTS: The mean serum zinc in the thalassemia patients (74.79 \pm 25.14 μ g/dl) was significantly lower compared to the control group (93.61 \pm 15.12 μ g/dl), ($p = 0.0001$). The serum zinc was not significantly different in thalassemia patients in terms of age, disease onset, gender, height, weight, body mass index, amount of blood transfusion, and type of chelation. There was a statistically significant correlation between serum zinc levels with a serum ferritin level of patients.

CONCLUSION: The study showed that thalassemia patients have significantly lower serum levels of zinc with no relation to medical factors.

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Introduction

In humans, thalassemia is considered one of the most common hereditary blood disorders [1], [2]. About 150 million people carry the gene of thalassemia worldwide. The disease most commonly is seen in Africa, the Mediterranean region, and South-east Asia. The incidence may be as high as 10% in these regions [3]. Iran and Iraq are among the countries with the highest prevalence of major thalassemia [4], [5]. The clinical features of the disease may not be obvious until a complete conversion occurs from fetal to adult hemoglobin (Hb). Typically, the switch is completed by the age of 6 months [3].

The most severe form of thalassemiias β -thalassemia major which requires frequent blood transfusions followed by giving iron-chelating agent (Desferrioxamine) [6]. Thalassemia is a group of inherited blood-borne disorders due to abnormal Hb chain synthesis (either alpha or beta chain). The lack of beta-chain synthesis causes beta-thalassemia, which causes the body to form new abnormal red blood cells (RBCs), leading to anemia. The abnormal Hb chain syntheses need about 200-point mutations in that particular chain of Hb. Beta-thalassemia major is a severe form of this blood disorder, where transfusion is the only hope for survival among patients, and a bone marrow transplant is a possible way to cure [3].

Zinc is an essential micronutrient for human health. It is vital for activating growth and physical and neurological development in infants, children, and adolescents. It is found in all parts of the body. It is a component in more than 300 enzymes and influences hormones. Zinc also accelerates cell division and enhances the immune system. It is vital in protecting the body from illnesses and fighting infections. It also participates in the metabolism of CHO, lipids, and proteins, which, in turn, leads to good food utilization. Zinc also enhances Vitamin D effects on bone metabolism [7].

Zinc deficiency observed in beta-thalassemia patients might have resulted in growth retardation through different mechanisms. Increased urinary zinc excretion has been described in thalassemia. Recent reports have suggested a link between increased urinary zinc excretion and renal tubular cell dysfunction in thalassemic patients [8]. There have been few studies of hyperzincuria in thalassemia major and its association with the iron chelator desferrioxamine, but, however, the results have been inconsistent [9].

Chronic blood transfusions in hemolytic disorders like β -thalassemia major may change the micronutrient status including zinc [10]. Zinc is a trace component, implicated in the synthesis of many other substances such as cholesterol, lipids and a lot of enzymes, immune, and antioxidant systems [11], [12]. Furthermore, it has an important role in protein synthesis,

cell division, wound repairing, and improving visual acuity [8]. Zinc has the main role in the RBC life cycle and its lack leads to increased RBCs breakdown [12].

Zinc deficiency could be a possible cause of delayed maturity in beta-thalassemia major patients [13], [14]. There is an evident gap in zinc status in patients with a β -thalassemia major in this region. Therefore, this study aimed to measure the serum zinc levels β -thalassemia major compared to a healthy control group. In addition, the role of medical and general characteristics on serum zinc level in β -thalassemia major was examined in this age-sex match study.

Patients and Methods

A total of 70 children previously diagnosed with β -thalassemia major (2–12 years) of both genders were included in this age- and sex-matched case-control study. The cases were matched for age and sex with 70 apparently healthy controls. The serum zinc concentrations were compared between cases and controls. The patients were included from Jin center in Duhok city. The healthy children were selected from Heevi Pediatric Teaching Hospital with no history of chronic diseases. The Jin center provides care for thalassemia patients in Duhok Governorate, Iraq Kurdistan. The data collection was done for a six month period between January 1 and June 30, 2017.

Inclusion and exclusion criteria

The patients who were diagnosed with β -thalassemia major up to 12 years old of both genders with no other medical chronic diseases met eligibility criteria for this study. The following children were excluded from the study; thalassemic children who were receiving multivitamins and Zn supplementation therapy, thalassemia children with any acute illness or any other chronic disease such as liver failure and heart failure.

Data collection and measurement

The following information was collected from the children and was recorded in a pre-designed questionnaire. The age, gender, onset age of disease (before one year and after one year), types of chelation (Desferrioxamine, Deferasirox (Exjade), Both Desferrioxamine and Deferasirox, or none). Body mass index (BMI) was categorized as normal, underweight, overweight, or obese.

To measure serum zinc, 3 ml venous blood was aspirated after cleaning the skin with a 70% alcohol swab. The blood was poured into a gel tube. Then, it was

centrifuged at 4000 rotation per minute for 10 minutes. The serum was separated and collected in a plain tube labeled numerically for the measurement of serum Zn using atomic absorption spectrophotometer with a normal range of serum Zn is 70–115 $\mu\text{g/dl}$, and serum ferritin with normal range (20–300 ng/dl in male and 14–150 ng/dl in females) [15]. The serum zinc levels were categorized as; normal serum zinc: 70–115 $\mu\text{g/dl}$, high serum zinc: >115 $\mu\text{g/dl}$, mild Zn deficiency: 50–70 $\mu\text{g/dl}$, and severe Zn deficiency: <50 $\mu\text{g/dl}$ [15].

Serum ferritin

Ethical considerations

The study was approved by the Ethical Committee of the Directorate General of Health/Duhok, Jin Center, and Heevi Pediatric Teaching Hospital. Written consent was obtained from the children's parents before the interviews were carried out.

The ethical approval of the protocol was obtained from the Council of the College of Medicine at the University of Duhok.

Statistical analysis

The homogeneity of children in terms of age and gender was examined in a Pearson Chi-squared test. The concentration of serum zinc was presented in mean (SD). The mean level of serum zinc between patients with β -thalassemia major and their controls was examined in an independent t-test. The significant level of difference was set at a $p < 0.05$. The statistical analyses were performed by Statistical Package for the Social Sciences version 25 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results

Table 1 shows that the thalassemia patients and their control were comparable in gender ($p = 0.864$) and age distribution ($p = 0.741$)

Table 1: Age and gender distribution

| Age (years) | Thalassemic patients | | Controls | | p-value |
|-------------|----------------------|------------|------------|------------|---------|
| | Male | Female | Male | Female | |
| 2–4 years | 9 (12.8) | 10 (14.2) | 8 (11.4) | 9 (12.8) | 0.741 |
| 5–9 years | 13 (18.6) | 20 (28.57) | 13 (18.6) | 20 (28.57) | |
| 10–12 years | 7 (10) | 11 (15.71) | 9 (12.8) | 11 (15.71) | |
| Total | 29 (41.42) | 41 (58.58) | 30 (42.85) | 40 (57.15) | 0.864 |

Pearson Chi-squared test was performed for statistical analyses

The mean serum Zn levels in thalassemic patients and controls

The serum zinc concentration in β -thalassemic patients was significantly lower

(Mean: 74.79 µg/dl) compared to healthy controls (Mean: 93.61 µg/dl; $p = 0.0001$), Table 2.

Table 2: The mean serum Zn levels in thalassemic patients and controls

| Study groups | Mean (SD) µg/dl | t-test | p-value |
|--------------|-----------------|--------|---------|
| Patients | 74.79(25.14) | -5.785 | 0.0001 |
| Controls | 93.61(15.12) | | |

An independent t-test was performed for statistical analysis.

The study showed that age of onset of disease, type of chelation, BMI, residence, and age have no association with serum zinc levels in β -thalassemic patients (Table 3).

Table 3: Association of patients' characteristics with serum zinc levels

| Characteristics | Zinc levels | | | | p-value |
|---|-------------|------|------|--------|---------|
| | Normal | High | Mild | Severe | |
| Age of onset | | | | | 0.35 |
| Below 1 year | 35 | 2 | 10 | 9 | |
| Above 1 year | 7 | 1 | 3 | 3 | |
| Type of chelation | | | | | 0.27 |
| Desferrioxamine | 0 | 0 | 0 | 0 | |
| Deferasirox (Exjade) | 36 | 3 | 12 | 10 | |
| Both desferrioxamine and deferasirox | 4 | 0 | 1 | 0 | |
| None | 2 | 0 | 0 | 2 | |
| BMI | | | | | 0.08 |
| Normal ≥ 18.5 and < 25 kg/m ² | 32 | 3 | 9 | 9 | |
| Underweight < 18.5 kg/m ² | 8 | 0 | 3 | 0 | |
| Overweight ≥ 25 and < 30 kg/m ² | 2 | 0 | 1 | 1 | |
| Obese ≥ 30 kg/m ² *** | 0 | 0 | 0 | 2 | |
| Residence | | | | | 0.47 |
| Urban | 26 | 3 | 8 | 5 | |
| Rural | 16 | 0 | 5 | 7 | |
| Age | | | | | 0.96 |
| 2-4 years | 16 | 0 | 5 | 5 | |
| 5-9 years | 18 | 3 | 3 | 6 | |
| 10-12 years | 8 | 0 | 5 | 1 | |
| Gender | | | | | 0.29 |
| Male | 19 | 3 | 3 | 4 | |
| Female | 23 | 0 | 10 | 8 | |

Zinc levels: Normal serum zinc: 70-115 µg/dl. High serum zinc: > 115 µg/dl. Mild Zn deficiency: 50-70 µg/dl. Severe Zn deficiency: < 50 µg/dl. National Institutes of Health, 2000. BMI: Body mass index.

The mean serum ferritin levels in thalassemic patients and controls

The mean serum ferritin in thalassemic patients was significantly higher compared to its concentration in the controls (3217.57 vs. 46.37 ng/dl; $p = 0.001$), Table 4.

Table 4: The mean serum ferritin levels in thalassemic patients and controls

| Variable | Mean (SD) ng/dl | t-test | p-value |
|----------|--------------------|--------|---------|
| Patients | 3217.57 (±2307.19) | 11.483 | 0.0001 |
| Controls | 46.37 (28.48) | | |

An independent t-test was performed for statistical analysis. serum ferritin with normal range (20-300 ng/dl in male and 14-150 ng/dl in females).

Correlation Between Serum Zinc and Serum Ferritin of Both Case and Control Group

There was a statistically significant correlation between serum zinc and serum ferritin of patients, while in controls, no significant correlation was noticed (Table 5).

Table 5: Correlation between serum zinc and serum ferritin of both case and control group

| Details | Serum zinc mean (SD) µg/dl | Serum ferritin mean (SD) ng/dl | p-value |
|----------|----------------------------|--------------------------------|---------|
| Patients | 74.79 (±25.14) | 3217.57 (±2307.19) | 0.006 |
| Controls | 93.61 (±15.12) | 46.37 (±28.48) | 0.915 |

An independent t-test was performed for statistical analysis.

Discussion

In this study, mean serum Zn was below the normal range in patients in comparison with the mean serum Zn level of the controls in agreement with the literature [16]. Although zinc deficiency is common in beta-thalassemia major patients, it has no significant effect on physical growth and frequency of infections [17].

A study aimed to identify the zinc status and its effect on the growth and functions of young beta-thalassemia major patients. They included 40 patients with beta-thalassemia major and compared to age- and sex-matched 30 healthy control. They found that the serum zinc level in beta-thalassemia major patients was 44.7 (SD: 24.2 µg/dl) compared to 63.3 (SD: 30.3 µg/dl) in the controls. The mean serum zinc level was significantly lower in patients compared to the persons in the control group. In agreement with the findings of our study, they reported that age, gender, blood transfusion duration, and volume, mean pre-transfusion Hb concentration, deferasirox dose, and serum ferritin level bear have not relation with serum zinc level in the patients group. Besides, serum zinc level was not found to associate with z-scores of stature, sitting, BMI, height index, and frequency of recent infections of patients [17].

Zinc deficiency in thalassemia major patients is determined by several factors, such as iron chelation therapy [18], ineffective erythropoiesis [19], increased hemolysis [19], and high prevalence of diabetes mellitus due to increased zinc losses [20].

Our study is consistent with the previous investigations [21], [22], [17]. In agreement with our study, several studies have shown that beta-thalassemia major patients have significantly lower serum zinc levels compared to healthy controls in the world [5], [14], [23].

Zinc deficiency in normal populations could be due to insufficient consumption of food sources rich with zinc and frequent consumption of tea. Dietary habits, geographical factors, and ethnic background may affect the serum zinc status in these patients may be contributory (Theodoridis *et al.*, 1998). Our patients were under deferasirox therapy as well, high prevalence of zinc deficiency could be explained by disturbances of zinc metabolism, renal dysfunction, and high urinary zinc excretion. Furthermore, poor dietary intake of micronutrients has been documented in children and adolescents with sickle cell diseases [24].

The prevalence of zinc deficiency is high in patients when comparing with normal healthy individuals; therefore, we can justify that the zinc deficiency in beta-thalassemia major patients could be further complicated by several factors. These factors are not specific to thalassemia disease. The variations in the geographical distribution of zinc content in the

soil, insufficient consumption of zinc-rich food sources, malnutrition, and genetic differences.

No significant relationship was found between serum Zn and other variables, such as age, gender, age of disease onset, weight, height, BMI, amount of blood transfusion, and type of chelation. This finding is consistent with studies that were carried out in other countries [23], [25]. It is worth mentioning at this point that there were some limitations of this study, such as the small numbers of patients and control group and the unavailability of data concerning diet regimens.

A significant difference ($p = 0.001$) was observed between the mean serum ferritin levels in thalassemic patients in comparison with the controls. This finding is consistent with a study carried out in Los Angeles, the USA which revealed a significant increase in ferritin in the patient group [26]. Several studies have reported that zinc bears no relation to iron chelation therapy, serum ferritin level, and blood transformation [23], [27], [28], [29]. However, Galleno and Sulthan reported that zinc deficiency is related to iron chelation therapy [30], [31].

Conclusion

The study showed that thalassemia patients have significantly lower serum level of zinc with no relation to medical factors.

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