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ORIGINAL ARTICLE

Effect of iron chelator desferrioxamine on serum zinc levels in patients with beta thalassemia major

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Abstract

β-thalassemia is the most common genetic disorder worldwide with an increased prevalence around the Mediterranean, Indian subcontinent and in South-East Asia. Various siderotic and non-siderotic complications significantly impact the quality of life. Thalassemic patients are also at risk of zinc deficiency due to diverse causes including desferrioxamine chelation. This study sought to investigate the prevalence of zinc deficiency in beta thalassemia major patients on desferrioxamine for iron chelation. *Study design:* This was a descriptive, prospective, cross-sectional study over a 6-month period. 63 cases of beta thalassemia major within the age group of 5-15 years on desferrioxamine for at least 1 year, were included. Basic patient demographics such as age, gender and duration of disease were recorded. Serum zinc levels were determined by atomic absorption spectrophotometry. *Results:* The mean age of patients was 10.84±3.47 (5 to 15) years. There were 35 (55.6%) males and 28(44.4%) females. The prevalence of zinc deficiency (zinc levels < 50 µg / dl) was 22.2%. Proportions of deficiency were higher in males with a duration of disease beyond 10 years. *Conclusions:* Zinc deficiency is not uncommon in beta thalassemia patients on desferrioxamine. We suggest that zinc levels be regularly monitored in these patients.

Key words: β thalassemia major, zinc deficiency, desferrioxamine.

INTRODUCTION

Beta thalassemia is a group of autosomal-recessive hereditary disorders characterized by genetic mutations resulting in reduced synthesis of β globin chains.[1] Over 200 different genetic defects have now been detected. The estimated prevalence of β thalassemia carriers in Pakistan is 5-8%.[2]

Thalassemia major patients often suffer severe transfusion-dependent anaemia. The severe imbalance of globin chain synthesis results in ineffective erythropoiesis, haemolysis and anaemia. Transfusion therapy,[1,3-6] which is the mainstay of treatment, allows for normal growth and development and suppresses ineffective erythropoiesis, but leads to iron excess.[1-3,5]

Excess iron causes oxidative injury and tissue siderosis. Hepatic, cardiac[5] and endocrinological siderosis[1-3] produces a variety of complications including diabetes,[1] hypothyroidism,[4] hypogonadism,[1,4] cardiac failure,[5,7] short stature and liver cirrhosis. Zinc deficiency,[1,3,6] osteoporosis, bone deformities and thromboembolism are other non-siderotic complications in these patients. Iron chelation treatment is necessary to prevent iron overload and subsequent damage to the internal organs. With appropriate iron chelation, patients with thalassemia major can live long lives if they have access to proper treatment.

Zinc deficiency[1,3,6] in thalassemia is due to various causes which include oral or intravenous iron chelation,[3] hyperzincuria and liver cirrhosis. Hyperzincuria is secondary to iron chelation.[3,6] The estimated prevalence of zinc deficiency in thalassemia major patients on desferrioxamine for iron chelation is 37%.[4]

Zinc is an essential trace mineral[8] required by all living tissues because of its crucial role both as a structural component of proteins and as a cofactor in enzyme catalysis.[8] Zinc is actively involved in many metabolic activities in the human body such as DNA synthesis, cellular growth, wound healing, protein synthesis, fertility and conception. The significance of zinc in human body metabolism is illustrated

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by the effects of zinc deficiency, which includes impaired wound healing,[8] diminished immune response,[8] growth retardation, influence bone mineral density, impaired glucose tolerance,[4] neurological disturbance,[8] irritability, deformed nails and increases the susceptibility of the patient to diverse pathogens.

The aim of this study is to determine the prevalence of zinc deficiency in beta thalassemia major patients between 5-15 years of age who are on desferrioxamine therapy, as zinc deficiency has not been reported locally and may be different in our thalassemic population as compared to international data.

MATERIALS AND METHODS

This was a descriptive, cross-sectional study carried out in the Department of Hematology, Liaquat National Hospital, Karachi from 1st Dec 2010 to 31st May 2011. Over the 6 months, 63 diagnosed cases of beta thalassemia major within the age group of 5-15 years on desferrioxamine for at least 1 year, were enrolled by non probability consecutive technique. The sample size was calculated to be n = 63 with P = 0.37% and d = 0.12%. The level of confidence is 95%. Basic patient demographics such as age, gender and duration of disease were recorded.

Patients on nutritional supplements, on oral zinc supplements, who have been on oral iron chelators, with acute infection, liver cirrhosis and malabsorption syndromes were excluded from the study. Patients with beta thalassemia intermedia and alpha thalassemia were also excluded.

Zinc assay

Blood samples were collected prior to transfusion. 5ml of peripheral venous blood were collected in sodium heparin containers and zinc levels were assessed by atomic absorption spectrophotometry. The zinc reference range in our population is 50-150 µg/dl.

Data analysis

Data was analysed using the SPSS windows version 13.0 statistical package. Results are presented as mean ± SD for age, gender, duration of disease and frequency of zinc deficiency. Stratification of age and gender was done to observe effects.

RESULTS

Demographic profile

Thirty-five (55.6%) of study subjects were male and 28 (44.4%) were females. The mean age of the patients was 10.84±3.47 years with a range of 5 to 15 years. The duration of disease ranged from 4.5 to 14.5 years, with a mean of 10.16±3.24 years. The mean duration of iron chelation therapy was 4.09±2.80 years. The descriptive statistics are shown in Table 1.

Zinc levels

The mean zinc level was 70.82±22.24 µg/dl and levels ranged from 30.4 to 117.0 µg/dl (Table 1). 14 (22.2%) patients were found to have zinc levels < 50 µg/dl (deficient) and 49 (77.8%) patients had zinc level between 50 - 150 µg /dl (non-deficient).

Of the category with zinc deficiency, the mean age was 11.35±3.49 years. 9(64.3%) were male and 5 (35.7%) were female, showing predominance of deficiency in male patients. The mean serum zinc in the deficient group was 43.1±5.9 µg/dl. Zinc deficiency was positively-associated with duration of chelation, the duration being 7.12±3.06 years and 2.95±1.45 years in zinc deficient and non-deficient patients respectively (P<0.001).

The serum zinc level was then observed with respect to age stratification. Patients were stratified into two groups based on age; 5 to 10 years (group 1) and 11 to 15 years (group 2). Both groups had almost equal number of patients: 31 (49.2%) patients stratified to group 1 and 32 (50.8%) patients to group 2. Of the 14

TABLE 1: Descriptive statistics of age, zinc levels and duration of disease (n=63)

	Age: years	Zinc levels: µg/dl	Duration of disease: years
Mean ±SD	10.84±3.47	70.82±22.24	10.16±3.42
95% Cl	9.96 -11.71	65.22 -76.42	9.30 -11.02
Median (IQR)	11 (7)	68.5 (37.4)	10 (6)
Range	5-15	30.4-117.0	4.5- 14.5

TABLE 2: Age group categorization of zinc deficient patients (n=14)

Zinc level	N	%	Age (years)	Mean ±SD (years)	95%Cl	Median (IQR)
Deficient <50µg/dl	6	42.9	5-10	11.35±3.49	9.33 to 13.37	12(5.25)
	8	57.1	11-15			

patients having zinc levels < 50 µg/dl, 6 (42.9%) patients were in age group 1 (5 to 10 years) and 8 (57.1%) patients belonged to group 2 (11-15 years) consistent with increased frequency of deficiency with increasing age beyond 10 years (Table 2).

DISCUSSION

In β thalassemia major, defective synthesis of beta globin chains results in accumulation of unpaired alpha chains.[9] The major cause of death is organ failure due to iron deposition. Hence, a main treatment strategy is to reduce the iron burden and promote the life expectancy of these patients. In this regard, the use of desferrioxamine has been the standard of care for many decades. However, iron chelation also removes various other essential elements including zinc. Desferrioxamine has zinc binding affinity and augments urinary zinc elimination and hyperzincuria,[3] culminating in gradual zinc depletion[3] and growth impairment[10] among other manifestations.

Zinc is not stored by the body, so it is important to eat foods that contain zinc every day to avoid a deficiency. These foods include red meat, poultry, oysters, shellfish, nuts, beans, whole grains, and fortified cereals. Zinc is also available in dietary supplements. To combat zinc deficiency, intervention strategies include zinc supplements, food fortification through the incorporation of zinc additives in food and dietary modification.

Studies from Iran,[3] Egypt[11] and California[12] have reveal pronounced zinc deficiency in patients on desferrioxamine for chelation while conflicting studies have been reported from Jordan and Tehran[13] which revealed high levels of zinc.

Our present study is in agreement with many regional and international studies, where a decrease in zinc levels have been detected in thalassemic patients. Shamshirsaz *et al*[1] from Iran reported that 79.6% of thalassemic patients had zinc deficiency. They investigated two hundred and twenty patients, and found mean zinc levels of 54.6±4.0µg/dl. The author attributed the cause of zinc scarcity to insufficient zinc intake, noting also that there was a high prevalence of deficiency of this trace mineral in the Iranian population.[1] However in comparison to Iranian thalassemic patients, we found a lower prevalence (22.2%) of zinc deficiency in our thalassemic patients.

Low levels of serum zinc have also been reported in thalassemia major patients compared to healthy participants from Egypt, by Nasr *et al*,[11] in a study of 64 patients. They also found that desferrioxamine treatment was associated with zinc deficiency. The mean zinc levels were significantly low, being 12.4±5.4µg/dl in patients while the control group showed 95.1±10.3 µg/dl. They also analyzed data for association of zinc insufficiency with duration of transfusion therapy or with duration of chelation therapy but no statistically significant correlation were established with these two factors.

Dehshal[3] from Iran reported zinc deficiency in 37% of thalassemia major patients. The author proposed that serum zinc levels be routinely monitored[3] in these patients. Likewise, Ferdaus *et al*[14] reported low serum zinc levels in 60% of Bangladeshi thalassemic patients. A regional study from India by Ghone *et al* revealed serum zinc levels of 94.06 ± 21.20 µg/dl in a control group compared to lower levels of 46.97 ± 8.40 µg/dl ($p<0.001$) in thalassemic patients.[15]

One Iranian study revealed relatively low (10%) prevalence of zinc deficiency in thalassemia major patients, while 52% had some degree of depression.[16] Other studies from Iran and Thailand show concurrent findings.[17,18]

In contrast to our results, Kwan and colleagues described that only 3 patients had zinc deficiency in their series of 68 patients.[19] Moreover Mehdizadeh *et al*[13] from Tehran have reported significantly higher serum zinc levels in 64 thalassemic patients. These findings may reflect

the impairment of zinc utilization in tissues in the pathogenesis of thalassemic patients. Lastly one study from Kuwait by Al Awadhi[20] established normal levels of serum zinc in 49 thalassemia major patients while noting that normal zinc levels may be related to non-compliance with chelation therapy.

We acknowledge many limitations of our study, including its observational nature and lack of a control group for comparison. Another limitation was the unavailability of data concerning the diet regime in our patients. Varying dietary habits and poor compliance for chelation therapy can also bias the results.

We recommend that future studies in Pakistan should also include details of dietary habits and nutritional supplements using a well-designed questionnaire, in order to address these confounders and also include a control group for comparison. Despite the limitations discussed above, the worthiness of this study is that this is first local study reported from Pakistan, and it provides essential local information for treatment and preventive strategies in the local setting.

Conclusion

This study revealed that hypozincemia is not infrequent in thalassemia major patients on desferrioxamine. We propose that analysis of serum zinc level be a regular feature of management in thalassemia patients treated with desferrioxamine. Prophylactic zinc supplements in the routine management in these patients should be considered.

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