Original Article

Serum Zinc Level in Thalassemia Major

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ABSTRACT

Objective: To compare serum zinc level between Thalassemia Major (TM) patients and normal population at Shafa Hospital in South West of Iran.

Methodology: A total of 25 male and 36 female of TM patients were enrolled in this study. Out of 61 patients thirty were treated by deferroxamine (DFO) and 31 were on the combination of DFO and deferiprone (DEF) protocol therapy. Sixty normal subjects of the matching age and gender were recruited as controls. From each patient and control group 2 ml of blood was taken in fasting condition. Cell blood count and serum zinc were carried out for both thalassemia patients and normal subjects.

Results: The mean age of patients and control group was 15±5years. Mean serum zinc level was 68.97±21.12µg/dl, 78.10±28.50 µg/dl, and 80.16±26.54 µg/dl in the TM with DFO, TM with DFO + DEF combination protocol and control group respectively. There was no significant correlation between patients and control group. However 50 percent of TM with DFO, 38.7 percent of TM with DFO + DEF and 32.8 percent of control group had hypozincemia.

Conclusion: Nearly 40 to 50 percent of TM patients and one third of normal subjects are suffering from hypozincemia. This study shows that low level of serum zinc is a health problem in both thalassemia patients and normal population in South West of Iran.

KEY WORDS: Zinc, Thalassemia Major, Deferroxamine, Deferiprone.

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INTRODUCTION

Thalassemia is the most common genetic disorder in the world that results in profound anemia. This disease is common in the Middle East and Iran particularly.[1] Iran is located on the zone of thalassemia and the country has more than twenty thousand TM patients. The prevalence of thalassemia minor is about 4 to 10 percent in the different parts of Iran.[2]

Treatment of thalassemia major is blood transfusion. The aim of treatment is to maintain pre transfusion haemoglobin equal or more than 9.5 g/dl. Blood transfusion induces iron accumulation. Removal of iron is a strategy treatment, iron chelator drugs such as DFO, DEF, deferasirox reduce iron burden and improve survival of thalassemia patients.[3] Many patients with thalassemia have deficiencies of micronutrients.[4] However, there is no consensus about zinc deficiency in TM patients.

Zinc is found in a wide variety of foods such as Oysters, red meat, poultry, beans, nuts, certain seafood, whole grains, fortified breakfast cereals, and dairy products and low in vegetable, fruits, tea, coffee, rice and bread.[5]

Zinc is an important trace element in animal and human nutrition and well established in synthesis of cholesterol, protein, and fats. Zinc is essential for more than 300 enzymes.[6,7] It has an important role in protein synthesis, cell division, wound repairing, improving visual acuity and immunity system, Zinc is crucial for taste perception, and a strong antioxidant as well.[8] Millions of people are suffering from zinc deficiency in the world, problem being high in developing countries. Signs of zinc deficiency include growth retardation, hair loss, diarrhea, delayed sexual maturation and impotence, eye and skin lesions, and loss of appetite.[9]

Delayed puberty and short stature is a great problem of TM, and most of them feel embarrassed facing their friends.[10] Some part of growth retardation seems to be related to zinc deficiency.[11]

Zinc is available in red blood cell membrane and plays an active role in survival of red blood cell. In the presence of zinc deficiency, red blood cell fragility will be increased. Zinc with antioxidant property can inhibit effects of iron free radicals while it's load is high in TM patients.[12]

For multiple reasons, hemoglobinopathies and thalassemia patients are prone to zinc deficiency.[13] The objectives of this study was to compare the zinc status in normal and thalassemia patients, difference between two arms of iron chelator drugs (DFO and DFO +DEF combination protocol) in inducing zinc deficiency, and whether to allow zinc supplementation to these patients routinely.

METHODOLOGY

The study was approved by ethics and university review boards committees of Ahwaz Joundishapur University of Medical Science. This descriptive cross sectional study was conducted at Shafa Hospital over a period of 6 months. Therefore, two arms of TM patients in the range of 10 to 20(mean: 15±5) years old were selected randomly. one arm consisted of 30 patients (15 male, 15 female) who were taking DFO with dose of 40 mg/kg over 8-12 hours subcutaneously of a minimum of five nights per week, and the other arm with numbers of 31(15 male, 16 female) were treated with a mean total daily dose of DEF 62 mg/kg(range 35-80) seven days a week, divided into three doses at least one hour before food along with DFO 40 mg/kg(range 20-50)/ over 8-12 hours subcutaneously of a minimum of two to four nights per week.

Informed consent was obtained from each patient and her/his parent (in non competent subjects) after the nature of the study was fully explained to them. A questionnaire including information about the demographic parameters, kind of iron chelator drug being used, recent infection, hepatitis C and B, usage of zinc supplement and hydroxyurea was completed for each patient.

Patients with history of recent infection, fever, diarrhea, hepatitis C and/or B, hydroxyurea taking dietary supplement containing zinc and non fasting state at the time of blood sampling were excluded.

Control group (n=60) was selected from matching normal subjects. In fasting state 2 ml of blood was drawn with plastic syringe from each patient and normal subject. After centrifugation at 3000 rpm for 10 minutes, separated sera were kept frozen at -70°C. Haemolysed sera were taken out of the study.

Serum zinc was measured by atomic absorption device model Carl Zeiss Jena (Jena, Germany) Model AAS3 flame atomic absorption spectrometer. A cut-off value of 70 µg/dl was used for serum zinc, samples below 70µg/dl was regarded as low (hypozincemia).[14] Based on the level of zinc we divided hypozincemia into four stages: I through IV 60-70µg/dl (I), 50-60 µg/dl (II), 40-50 µg/dl (III), <40 µg/dl (IV).

After collecting data, statistical analysis was performed by SPSS 16.0.2. Values were presented as means ± 2 SD. Differences were considered significant at $P < 0.05$. Laboratory observer and data analyzer had not any idea about the relationship of samples to patients or normal subjects.

RESULTS

Mean serum zinc level was 68.97±21.12µg/dl (range: 21-107) in TM with DFO therapy. TM patients with DFO+ DEF combination protocol had mean serum zinc level of 78.10±28.50µg/dl (range: 27-146).The mean serum zinc level was 80.16±26.54 µg /dl (range: 25-146) in normal subjects. Nearly 50 percent of TM with DFO, 38.7 percent of TM with DFO + DEF combination protocol and 32.8 percent of control group had hypozincemia. The frequency of hypozincemia in three groups in respect to gender is shown in Table-I.

Table-II shows the Frequency of Severity of hypozincemia in two arms of TM and normal group. There was no significant correlation between zinc level of any group of patients and normal subjects ($P > 0.05$) [(except male thalassemia patients with DFO

Table-I: Frequency of percent hypozincemia in two groups of patients and normal population by gender.

	Percent of hypozincemia	
Type	*Male*	*Female*
TM with DFO	66.7%	42.9%
TM patients with DFO+ DEF combination protocol	40%	37.5%
Normal control	26.5%	41.7%

There was no significant correlation between two arms of patients and normal control (P >0.05) except for male group of TM with DFO comparable with normal control (P<0.03).

Table-II: Percent of severity of hypozincemia in thalassemia major patients and normal group.

	Percent of Severity of hypozincemia			
Type	*I*	*II*	*III*	*IV*
TM with DFO	16.66%	13.33%	16.66%	3.33%
TM patients with DFO+ DEF combination protocol	12.90%	12.90%	3.22%	9.67%
Normal control	10.34%	10.34%	6.89%	5.17%

There was no significant correlation between four groups of patients and normal control (P >0.05) except in TM with DFO for group IV comparable with group I and III. (P<0.03)

in comparison with normal group (P: 0.03)]. Low zinc level in both arms of TM are more prominent in male than female, but in normal population it was vice versa.

DISCUSSION

The major contributing factors of zinc deficiency in TM are multiple and include: hyperzincuria induced by hemolysis and iron chelator drugs, Low intake of enriched zinc foods due to anorexia and fear of increasing iron, impaired zinc reabsorbtion in renal tubules. Folic acid may reduce zinc absorption when zinc intake is low. Other factors that affect serum zinc levels in normal population, such as dietary habits, geographical factors, and ethnicity, may also have an impact in TM.[15-17] On the other hand, replacement of defective red blood cells with normal blood and correction hemolysis that is established by regular blood transfusion may reduce hyperzincuria. Rea et al suggested hyper transfusion can prevent zinc deficiency in TM and therefore, due to irregular blood transfusion in TM and thalassemia intermediate the prevalence of zinc deficiency is high.[18]

Thalassemia patients with liver fibrosis and cirrhosis may have some degree of low serum zinc level. Soomro et al showed 69% of cirrhotic patients have hypozincemia.[19]In thalassemic patients with liver injury the release of somatomedin C is low. Zinc supplementation may increase the production of somatomedin C from liver of TM patients.[20,21]

In our study the mean serum zinc level was nearly close in three groups (two arms of TM and normal group).There was no significant correlation between two arms of patients and normal control (P >0.05) except for male group of TM with DFO comparable with normal control (P<0.03). We could not find any justification for this issue. We did not find any significant relation between serum zinc status in two arms of patients and control group, because 32.8% of control group had zinc deficiency.

With respect to reference cut-off point of serum zinc level (70 µg/dl)[14], we found 50%, 38.7% and 32.8% hypozincemia in TM with DFO, TM with DFO+DEF and normal control respectively. We expected low level zinc in TM patients, but 32.8% of low zinc level in normal population indicates a health problem in our province. Hypozincemia similar to iron deficiency anemia needs to be considered as a nutritional problem in Khuzestan province.[22] In another study, the researchers found 35-65% of zinc deficiency among healthy children and adolescents in Iran.[23]

In 1997 Stefano et al showed the low level of zinc in thalassemia patients is considered a problem with DFO.[24] The other studies confirmed these results.[25,26] However, many studies have reported contrary to these findings.[11,27]

In a study in the north of Iran, TM patients with appropriate blood transfusion and DFO injection had high urine zinc concentration and normal serum zinc level. This indicates that blood transfusion is more important than Desferal injection.[25]

Bekheirnia et al reported that frequency of hypozincemia in TM patients was higher than our study (85.5%vs 50%). Similar to our findings they also observed more prevalence of hypozincemia in males than females.[28] However Moafi et al reported the prevalence of Zinc deficiency in TM patients as 10%, which was very lower as compared to our study.[29]

Rea, Donma and Mehdizadeh et al all interestingly, found that the mean serum zinc level was significantly high in thalassemic group. These studies indicated that zinc deficiency in thalassemic patients who were on regular blood transfusion was rare and they showed that routine zinc supplementation is not necessary for most of TM patients.[11,18,30]

As regards other studies, our findings are comparable with some researches[28,30] and completely opposite to some studies.[11,31] The different results may be related to patients nutritional status. As much a comprehensive research study among thalassemia patients considering nutritional and growth indices in different parts of Iran is recommended.

CONCLUSION

In our study the frequency of low zinc level in two arms of TM patients and control group was considerable. This research shows that though routine indication of zinc supplement in TM is questionable, but, periodic serum zinc measurement is recommended.

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