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Original Research Article

Status of trace elements zinc, copper, and selenium in transfusion dependent beta thalassemic Indian children: a cross sectional study

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ABSTRACT

Background: Maintenance of normal levels of copper, selenium, and zinc play an important part in lessening the morbidities associated with thalassemia major. Levels of these elements have been found to be altered in this chronic transfusion dependent disease from all over the world, but with widely variable results. Besides repeated blood transfusions and use of chelating agents, their levels in thalassemics are affected by genetic and dietary factors also, compelling us to undertake this study in our population. The objectives of this study were assessment of serum levels of zinc, copper and selenium in transfusion dependent beta thalassemics.
Methods: Cross sectional descriptive study conducted at Thalassemia Day-care Centre of a teaching hospital. Total 64 transfusion dependent thalassemics in the age group 3-18 years were subjected to serum levels of zinc, copper and selenium by inductively coupled plasma mass spectrometry technique.
Results: Four (6.25%) had hypozincemia, 15 (23.43%) hypocupremia and one (1.565%) had hypercupremia. Two (3.12%) had higher selenium levels (>190 µgm/l).
Conclusions: In contrast to previous studies, hypocupremia has been found to be more prevalent than hypozincemia and hyposelenemia in our population.

Keywords: Copper, Selenium, Thalassemia, Trace elements, Zinc

INTRODUCTION

In India around 10000 children are born with beta thalassemia major every year.[1] Chronic hemolysis, repeated blood transfusions, endocrinopathies, genetic and dietary factors and use of chelating agents alter the levels of many major and micronutrients in these patients. Among the trace elements mainly iron, zinc, copper, selenium, magnesium, chromium and iodine are affected in hemoglobinopathies.[2-5]

Ubiquitous presence of zinc in cells makes it the second most abundant trace metal in human body after iron. It is required in the functioning of over 300 catalytic enzymes and is considered essential for cellular proliferation and differentiation through its role in the folding of DNA-binding domains of transcription factors and as an integral component of RNA polymerase.[6,7] In thalassemics zinc deficiency has been linked to reduced physical growth, low bone mass and impaired glucose tolerance test.[8]

Copper is also found in almost every cell of human body, with the highest concentration attained in brain and heart tissues.[9] It acts as a cofactor for over 30 enzymes and being an integral component of superoxide dismutase and ceruloplasmin, it protects the cells from free radical damage also.[10] In thalassemics copper deficiency has been associated with growth retardation and delayed sexual maturity.[11]

Selenium is a component of glutathione peroxidase and iodothyronine deiodinase enzymes and also incorporates in various important proteins such as hemoglobin and myoglobin.[12] In one study, low dose selenium supplementation in thalassemics has been shown to enhance the NK cell activity.[13]

It is clear that maintenance of normal levels of these elements play an essential role in lessening the morbidities associated with β thalassemia. Though previous studies are available on the status of these nutrients in thalassemics from other countries, but results are conflicting. Here we aimed to assess the need for supplementation of these nutrients in our population affected with thalassemia.

METHODS

It was a cross sectional descriptive study conducted at Thalassemia Day-care Centre of a teaching hospital. After obtaining informed written consent from the parents/guardians, sixty four transfusion dependent children affected with beta thalassemia in the age group of 3-18 years were randomly selected from the record register for the study. Patients with liver or renal dysfunction or gastrointestinal diseases were excluded. Institutional ethics committee approved the study. Clinical and paraclinical details including age, weight, height, average hemoglobin of last 6 months and average blood requirement of last one year were recorded in a predesigned format. Non-fasting 5 ml venous blood sample was obtained in the morning just prior to due blood transfusion to measure serum levels of zinc, copper and selenium by inductively coupled plasma mass spectrometer (ICP-MS) X series-II, manufactured by Thermo Fischer Scientific India, Mumbai. As per the laboratory, normal serum levels of these elements were defined as; for zinc >650 µ gram/liter, and >700 µ gram/liter (3-9 years and more than 10 years age group respectively) (International Zinc Nutrition Consultative Group (IZiNCG), 2004), for copper 900-1900 µ gram/liter and for selenium 23-190 µ gram/liter (Tietz Clinical Guide to Laboratory Tests, Fourth Edition by Alan H.B. WU. Saunders, Missouri (2006).

Statistical analysis was performed using computer software (SPSS version 20). The qualitative data were expressed in proportion and percentages and for quantitative data Shapiro-Wilks test was applied to assess normality of distribution; non-gaussean data were presented as median with inter-quartile range. Spearman's rank correlation coefficient was calculated to express the relationship between two quantitative variables. For all calculations both side tail p value <0.05 was considered significant.

RESULTS

A total of 64 children were included in the study, out of which 28(43.75%) were more than 10 years old, 25 (39.06%) were 5-10 years of age and 11(17.18%), belonged to under five age group. Males outnumbered females (37 vs 27 respectively) with a sex ratio of 1.37:1. Among more than five years age group three (5.66%) children had BMI less than 3rd centile (as per IAP growth curves 2015). Among 3-5 years age group two (18.18%) children had weight for height less than 3rd centile (IAP charts 2015). Dispersion of data pertaining to clinical and para-clinical parameters has been summarized in Table 1.

Four (6.25%) had hypozincemia, 15 (23.43%) hypocupremia and one (1.565%) had hypercupremia. Two (3.12%) had higher selenium levels (>190). Dispersion of data related to these parameters has been summarized in Table 2.

Table 1: Clinical and paraclinical characteristics of study cohort.

Characteristics	Range	Mean (SD)	Median (IQR)
Age (years)	3-18	9.96 (4.37)	9 (3-18)
Weight (Kg)	9-57	25.34 (10.76)	23 (16-23.75)
Height (meter)	0.87-1.71	1.25 (0.20)	1.27 (1.09-1.41)
Average Hb of last 6 months (gm/l)	52-93	78.3 (7.4)	79.5 (72.2-84.7)
Blood requirement in last one year (ml)	152.8-324.4	236.01(43.76)	228.6 (202.26-262.26)

Table 2: Serum levels of elements.

Serum levels of element	Range	Mean (SD)	Median (IQR)
Zinc (µgram/l)	500.1-1898.8	939.85 (211.27)	924.85 (793.65-1038.5)
Copper (µgram/l)	188-1953	1049.03 (276.16)	1027 (899.37-1195)
Selenium (µgram/l)	33.6-222.4	89.64 (35.11)	83.9 (67.22-96.37)

No correlation was noted between serum levels of these elements and age or blood requirement (p>0.05) (Table 3).

Table 3: Correlation of element's levels with age and blood requirement.

Serum levels of	Spearman for age	Spearman for blood requirement
Zinc	0.130 (0.302)	0.0733 (0.564)
Copper	-0.361 (0.003)	-0.123 (0.328)
Selenium	0.111 (0.382)	0.242 (0.0532)

Figure in parenthesis denotes p value for Spearman correlation co-efficient

DISCUSSION

Authors found hypozincemia in only 6.25% of our population, but prevalence of hypocupremia was much higher (23.43%). None in our group had hyposelenemia. Our study had certain limitations like small group, non-availability of dietary data. In the absence of control group from the same population, these nutritional deficiencies cannot be solely attributed to thalassemia. Previous studies have compared the serum zinc level in thalassmics and their control population but results are conflicting; serum zinc level were comparable in both the thalassmics and their siblings in Pakistani children (median serum zinc level - 1000 vs 920 µ gm/l vs respectively) lower in thalassmics in comparison to control.[14] In Egypt and Iraq (882.8±177.6 vs 1135±153.9 and 386.5±202.5 vs 964.4±276.3 µgm /l respectively) and were higher in thalassemics in comparison to control in Jordan (2208±113 vs 1053±120.1 µ gm/l respectively).[5,15,16] In the present cohort median serum zinc level was found to be 924.85 µ gm/l.

In Iranian thalassemics the prevalence of hypozincemia (zinc concentration under 700 µg/l) has been found to be very high (65%-100%) in contrast we could find it only in 6.25% of our population.[4] Hypzincemia in thalassmics has been attributed to proximal tubular damage, hyperzincuria following hemolysis, chelating effects of deferoxamine and deferiprone and increased ferritin levels and hyperzincemia to cirrhotic changes, owing to hemosiderosis and abnormal glomerular filtration rate.[16-21.] In contrast some of the studies did not find any specific influence of thalassemia on zinc levels, rather they related it to genetic, environmental or dietary factors.[22]

Copper

Results of serum copper levels are again variable. In the present study mean copper level was found to be 1049.03±276.16 µ gm/l and 23.43% children displayed hypocupremia (level less than 900 µ gm/l) and 1.56% hypercupremia (more than 1900 µ gm/l). Almost similar findings were noted in Iran also (mean level 958.4±480.1 µ gm/l, deficiency in 32.1% and excess in 45.9%), but their normal range was different than ours (700-1500 µ gm/l vs 900-1900 µ gm/l respectively).[11] Another study from the same region reported serum copper level of 1524.2±241.7 µg/l with deficiency in none.[4] In contrast In Jordan and in Iraq serum copper levels were found to be raised in comparison to control (1899.2±737 vs 1086.1±133.3 µ gm/l and 1621.0±509.2 µ gm/l vs 1017.5±259.8 respectively).[5,16] Increased gastrointestinal absorption and repeated blood transfusions induced hepatic parenchymal damage are the major contributors of hypercupremia in thalassemics.[5,10] In addition, kidney function, copper to zinc ratio and administration of deferroxamine also play the role in maintaining serum copper levels.[23-25]

Selenium

In the present cohort mean selenium level was 89.64±35.11 µ gm/l. Considering normal selenium level to be 23-190 µ gm/l, none of our child had hyposelenemia but 3.12% had hyperselenemia. The findings observed in Iran were slightly different, selenium deficiency in 25.52% and excess in 39% with a mean level of 158.0±85.2 µ gm/l but in their study normal range taken was different (95-140µgm/L).[26] In a study from Egypt selenium levels were found to be lower than control (31.5±19.1 microg/l vs 65.9±6.3, p <0.001).[10] Similar to us age, and number of transfusions did not influence the serum levels of zinc, and selenium in the studies by Mashadi and Mahyar, but additionally they also demonstrated no effect of types of chelators on the levels of these elements. Poor negative correlation between age and serum copper levels in our study are contradictory to their findings.[4,26]

These wide variability in results could be because of differences in ethnicity, dietary habits, drugs for chelation, frequency of blood transfusions, age group, BMI, sample size (affecting power of study), machines and techniques used for measurements, range of normal levels, degree of liver and renal dysfunctions. In comparison to most of the previous studies prevalence of hypozincemia has been found to be very low in the present study, thus obviating the need of routine zinc supplementation. The same stands true for selenium also. Higher prevalence of hypocupremia stresses the need for its routine supplementation, but being a potentially toxic metal, its level need to be monitored closely. Further being a single center study on a small group, these results cannot be generalized. Seeing a wide variability in results from across the world, multi-center trials on supplementation of these trace elements are required to reach any conclusion. Take home message: serum levels of zinc, copper and selenium should be checked before routine supplementation in thalassmics.

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