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Serum zinc, copper and ferritin levels in transfusion dependent thalassemia patients with iron chelator therapy

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Abstract

Background: Transfusion dependent thalassemia (TDT) patients require regular blood transfusion and iron chelator therapy to maintain their life. Iron chelator may alter serum zinc and copper level in TDT patients. **Objective:** To observe serum zinc and copper and ferritin levels in transfusion dependent thalassemic patients treated with iron chelator. **Method:** The present cross sectional study was carried out in the department of Physiology, BSMMU, Dhaka between September 2017 to February 2019. Thirty cases of TDT, aged 5-40 year were included in the study group. Age and sex matched 30 healthy subjects were also studied as control. All the TDT patients were selected from the outpatient Department of Hematology and Transfusion Medicine, BSMMU, Dhaka. Serum zinc was measured by Spectrophotometric method and serum copper and ferritin levels were measured by colorimetric method. For statistical analysis independent sample t test was used. **Result:** The mean serum zinc level was significantly ($p<0.05$) lower and serum ferritin level was significantly ($p<0.001$) higher in TDT compared to control. Again, mean serum copper level and Zn/Cu ratio were not significantly ($p>0.05$) different in study groups compared to that of control. In addition, 3.3 % TDT patients had hypozincemia and 13.3% TDT patients had hypercupremia. **Conclusion:** This study may conclude that low serum zinc level and high copper level may be associated with TDT patients treated by combined deferoxamine (DFO) & deferiprone (DFP) iron chelator.

Key words: TDT, zinc, copper and iron chelators (DFP and DFO)

Introduction

Thalassemia is a group of autosomal recessive hereditary blood disorder in which there are defective synthesis of alpha or beta globin subunit of hemoglobin.[1-2] About 150 million people carry the thalassemia gene worldwide[2-3] but it is most common in Mediterranean regions, Middle East, part of Africa, Central Asia, India sub-continent, Southern China and into the Pacific island[3-4]. According to World Health Organization, about 3% of population is carrier of beta thalassemia and about 4% population is carrier of Hb-E in Bangladesh[5-6].

The principal treatment of thalassemia involve blood transfusion to correct anemia[1].The repeated blood transfusion may lead to accumulation of excess iron in the body[3] causing oxidative stress and organ damage[4-5]. The most common cause of death is heart failure due to transfusional iron overload[1]. So, several iron chelators have also been used to remove the excess iron from the body[3]. Currently there are three approved commercially available iron chelators – deferoxamine (DFO), deferiprone (DFP), deferasirox (DFX)[7].

Ferritin binds with iron and stores excess iron within the cell and iron overload causes high concentration of serum ferritin. Therefore, estimation of serum ferritin is most commonly used to evaluate iron overload in patients with thalassemia [8-10] .

Among minerals, zinc is essential in many biological processes. Zinc act as a cofactor for more than 300 enzymes and it is actively involved in DNA synthesis, cellular growth, wound healing, protein synthesis, fertility, conception, immune system and metabolism. It has antioxidant properties also [4,8,11-12]. Zinc deficiency causes growth retardation, hypogonadism, infection, impaired wound healing, decreased bone mineral density, impaired glucose tolerance, neurological disturbance etc.[1,11].

In our body, copper is widely distributed in tissues in the form metalloproteins acting on enzymes[12].Copper is the major component of hemoglobin and required for production of hormone. It has also antioxidant properties[11]. It acts as a co-factor of enzymatic reaction including cytochrome c oxidase, lysyl oxidase, superoxide dismutase, catalases, thyroginase and glutathione peroxidase[4]. Excess copper is responsible for vomiting, hypotension, maelena, gastrointestinal disturbance and wilson's disease [1,11]. Data on these minerals in TDT patients treated with iron chelator is very scarce. Therefore, this study has been designed to evaluate zinc and copper and ferritin levels in TDT patients treated with iron chelator.

Methods

The present cross sectional study was carried out in the department of Physiology, BSMMU, Dhaka between September 2017 to February 2019 and protocol of this study was approved by Institutional Review Board, BSMMU. Serum zinc, copper, ferritin and Hb levels of 30 TDT patients treated with combined iron chelator (DFP) and (DFO) and 30 healthy subjects (control), age ranged from 5-40 years were assessed. TDT patients were selected from outpatient Department of Hematology and Transfusion Medicine, BSMMU and control were selected among the relatives and attendants of patients, hospital staff and subjects available in the BSMMU campus and also by personal contact. Subjects with history of renal disease, any acute and chronic disease, vitamins and minerals supplementation were excluded from the study. After selection of the subjects, the purpose of the study was explained to each subjects and informed written consent was taken. Detailed family and medical history, anthropometric measurement were recorded. For estimation of serum copper, zinc, ferritin and Hb levels 5 ml of venous blood was collected from ante-cubital vein under aseptic precaution from each subjects and serum was prepared for these biochemical

tests. Serum zinc was measured by Spectrophotometric method and serum copper and ferritin was measured by colorimetric method. Data were expressed as Mean±SE. Data analysis was done with SPSS version 16. For statistical analysis independent sample t test and Chi-Square test were performed.

Results

In this study, all the groups were matched for age and sex but BMI ($p<0.05$) and Hb ($p<0.001$) were significantly lower in TDT compared to that of control (Table I). Mean serum zinc level was significantly ($p<0.05$) lower and mean serum ferritin was significantly ($p<0.001$) higher in TDT patients compared to that of control. There was no significant difference in mean serum copper and Zn/Cu ratio between TDT and control subjects (Table II).

Again, in this study 3.3 % TDT patients had hypozincemia and 13.3% TDT patients had hypercupremia. No control had hypozincemia or hypercupremia (Table III)..

TableI: Age, BMI and Hb in both groups (N=60)

Parameter	Control (n=30)	TDT (n=30)
Age (years) Mean±SE	19.86±1.57	19.66±1.68
Male no(%)Female no(%)	15(50%)15(50%)	15(50%)15(50%)
BMI(Kg/m^2) Mean±SE	21.87±0.89	18.54±0.56*
Hb (g/dl) Mean±SE	13.75±0.19	7.78±0.36***

Statistical analysis was done by independent sample t test and Chi-Square test.BMI-Body mass index;Hb-Hemoglobin; TDT-Transfusion dependent thalassemia;*p<0.05, ***p <0.001.

Table II: Serum zinc, copper, zn/cu ratio and ferritin levels in both groups (N=60)

Parameter	Control (n=30)	TDT (n=30)
Serum zinc (mg/L)	0.78±0.01	0.70±0.01*
Serum copper (µg/dl)	98.90±5.23	100.70±5.98
Zn/Cu ratio	0.009±0.001	0.008±0.001
Serum ferritin (µg/L)	40.39±7.68	6276.85±709.82***

Data are expressed as Mean±SE. Statistical analysis was done by independent sample t test.TDT-Transfusion dependent thalassemia; *p<0.05, ***p <0.001.

Table III: Frequency of subjects by hypozincemia, hypercupremia in both groups (N=60)

Parameters	Control (n=30)	TDT (n=30)
	no. (%)	no. (%)
Hypozincemia	00 (0)	1 (3.3)
Hypercupremia	00 (0)	4 (13.3)

Data are expressed as no. %. TDT-Transfusion dependent thalassemia. Cut point for zinc-.55mg/L cut point for copper- 155 microgram/dl

Discussion

The present study observed serum zinc and copper and ferritin levels of TDT patients treated with combined iron chelators.

The result of this study showed significantly lower serum zinc level in all TDT patients than control. Similar observation were published by others[13-14]. On the other hand, normal serum zinc level was observed in TDT patient treated with DFP and DFO iron chelator separately [8,15]. In the present study, serum copper level of TDT was not significantly different than control. But Mashhadi found lower level of serum copper in TDT patients treated with combined iron chelator and Genc et al. also found similar result in patients treated with DFP iron chelator[8,16]. Moreover, significant number of TDT in this study were suffering from zinc deficiency and excess copper.

The presence of Zn deficiency, Cu excess in the TDT patients under combined chelator therapy cannot be explained from this study. The body of literature suggested that decreased serum zinc level may be due to variation of stability constant of different metal ions. It has been found that the stability constant of zinc and iron are16.1 and 14.4 respectively. Metal with higher stability constant competes with metal of lower stability constant for the chelating agent. As the stability constant of zinc is higher than iron, so zinc can first bind to iron chelator despite of presence of excess iron causing removal of zinc from the body resulting in their deficiency[17-18].

It has also been suggested that it may be caused due to inverse relationship between zinc and copper. Zinc deficiency is associated with elevated serum copper level as zinc interfere copper absorption and it induce synthesis of intestinal metallothionein. Metallothionein binds with copper causing decreased absorption of copper from intestine and increased fecal excretion. When there is zinc deficiency, metallothionein and ceruloplasmin are also deficient causing increased serum copper level[18-21].

Conclusion

From the result of the study, it may be concluded that low serum zinc and high serum copper may occur in TDT patients treated with combined (DFP &DFO) iron chelator. So, routine estimation of serum zinc and copper levels may be useful to prevent the harmful effect of alteration of these micronutrient concentrations in TDT when patients treated with combined iron chelator.

Conflict of interest None.

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