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ORIGINAL ARTICLE

Growth Parameters in Children with Transfusion-Dependent Thalassemia and Their Correlation with Serum Ferritin

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Abstract

Background: *Thalassemia represents one of the most common hereditary genetic disorders in Bangladesh. Impaired growth is seen in children with transfusion-dependent thalassemia which is thought to be the consequence of iron overload. Growth retardation affects the quality of life.*

Objective: *To assess growth parameters in children with transfusion-dependent thalassemia and their correlation with serum ferritin.*

Methods: *This cross-sectional study was carried out on 67 transfusion-dependent thalassemia patients aged between 5 to 18 years who attended the Department of Pediatric Hematology and Oncology and the Department of Transfusion Medicine in Bangabandhu Sheikh Mujib Medical University (BSMMU) from June 2020 to August 2021. Anthropometric measurements of children including age, sex, weight, and height were recorded, and Z scores and BMI were calculated. Serum Ferritin level was estimated for each of the participants. Statistical analysis of the results was obtained by using Statistical Packages for Social Sciences (SPSS version 22).*

Results: *More than one-third of children with Transfusion-dependent thalassemia were underweight (44.7%) with stunted growth (40.3%). The mean serum ferritin levels were 2819.04±1085.48µg/l and 2913.44±1304.53µg/l in the beta-thalassemia and E-beta thalassemia groups respectively. The mean serum ferritin level was 2807.0±1271.9µg/l in normal weight, 2995.7±987.0 µg/l in underweight, and 3000.0±1504.7 µg/l in severely under-weight according to WAZ score. Similarly, the mean serum ferritin level was 2889.34±1209.2 µg/l in normal height, 2836.73±955.0 µg/l in stunted, and 2908.33±1415.2 µg/l in severely stunted according to HAZ score. The mean serum ferritin level was 2819.04±1085.48µg/l in BMI <5th percentile and 2913.44±1304.53µg/l in BMI 5th to 85th percentile. The difference was not statistically significant (p>0.05).*

Conclusion: *There is no correlation between growth parameters with serum ferritin levels in children with transfusion-dependent thalassemia.*

Keywords: *BMI, growth parameters, serum ferritin, transfusion-dependent thalassemia.*

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Introduction

Thalassemia major is one of the most common genetically transmitted diseases in the world and is associated with reduced synthesis of structurally normal hemoglobin.[1] In post-uterine life, two types of hemoglobins predominate, hemoglobin A1 and hemoglobin A2. Both of these are made up of four tetramers, either two α globins and two β globin (hemoglobin A1) or two α globins and two δ globins (hemoglobin A2). In addition, a small percentage of fetal hemoglobin (HbF) is present and is made up of two α globins and two γ globins.[2] Thalassemia major is a heterogeneous disease presenting during infancy or early childhood. Although thalassemia is preventable by premarital counseling and prenatal testing, a large number of children are born with thalassemia, and curative treatment in the form of bone marrow or stem cell transplantation is not possible for the majority of these patients. Patients need regular transfusions of packed red blood cells (PRBCs) and iron chelation along with close monitoring and treatment for complications of the disease.[3] There were 9.8 million thalassemia carriers in Pakistan with an approximate carrier rate of 5-7%. The definitive cure for transfusion-dependent thalassemia is bone marrow transplantation.[4] However, this is not a cost-effective option for the majority of patients in an underprivileged society. The survival of the patients, therefore, depends on regular blood transfusions and iron-chelating therapy.[5] Despite being an effective treatment there are many serious long-term complications. Iron toxicity (hemosiderosis) is one of these devastating complications with consequential end-organ damage and stunted growth.[6] Growth retardation is multifactorial and the etiology varies with age. The authors stated that chronic hypoxia, nutritional deficiencies (of zinc and folate), and iron toxicity are the main contributors in early childhood.[7] Iron, as well as chelation toxicity, hepatitis, psychosocial issues, and endocrinopathies (hypogonadism, hypothyroidism, and growth hormone failure), are the etiological factors for delayed or absent pre-pubertal growth spurt.[8,9] Researchers reported that chronic anemia increases erythropoietin secretion, marrow expansion, and thinning of bony cortices as well as increases RANKL with a negative effect on bone formation.[10] They also detailed that excessive iron interferes with the maturation of osteoid and deposits in hydroxyapatite crystals thus interfering with normal bone metabolism. Similarly, deferoxamine (iron chelator) inhibits DNA synthesis, proliferation, and maturation of fibroblasts and osteoblasts. These factors have detrimental effects on bone mineralization and can also compromise physical growth in thalassemia.

A study reported that approximately one-third (33.11%) of patients with transfusion-dependent thalassemia major were of short stature. In this group of patients with pretransfusion Hb levels maintained at desired levels and physical growth was correlated with the status of iron overload.[3] They also suggested that regular blood transfusions can maintain pretransfusion Hb levels, but if serum ferritin levels are higher than the desired levels, the patient's physical growth can be affected. Thus, along with maintaining Hb levels, it is important to have effective iron chelation therapy to minimize retardation of growth in patients with transfusion-dependent thalassemia. Iron overload is associated with many side effects such as Hypogonadotropic hypogonadism, pituitary gland abnormalities, growth hormone deficiency, and various organ damage. Thalassemia patients requiring regular blood transfusions need regular monitoring of serum ferritin and better strategies for removing excess iron from their bodies. Considering the facts and figures, the present study is aimed at growth parameters in children with transfusion-dependent Thalassemia and their correlation with serum ferritin.

Materials and Methods

This cross-sectional study was carried out in 67 children with transfusion-dependent thalassemia (beta-thalassemia major and Hb E/ beta-thalassemia) who attended the Department of Pediatric Hematology and Oncology, BSMMU, Dhaka, from June 2020 to August 2021. Children aged from 5 years to 18 years, diagnosed with Thalassemia by Hb-electrophoresis and Transfusion dependent Thalassemia were enrolled. Patients with chronic kidney disease, chronic gastrointestinal disease, chronic liver disease, and chronic hemolytic anemia apart from thalassemia were excluded from this study. Ethical clearance was taken from the local Ethical Committee to perform the investigation and study. All the legal guardians of participants were properly explained about the objectives of the study along with its procedure, risks, and benefits to be derived from the study in an easily understandable local language and then informed consent was taken from them. It was assured that all records would be kept confidential and would not be disclosed. It was also assured that the procedure was helpful for both the physician and patients in making a rational approach regarding the management of the patient. After taking history and clinical examination all the patients were having standard monitoring. All findings were collected in a pre-designed data collection sheet.

For assessing growth status; age, sex, weight, height, and Z score were recorded. Body mass index (BMI) was calculated. Weight was measured in kg using an electric digital scale and its accuracy was periodically

verified using reference weights.Height was measured in cm. Children were measured on scales with height gauges, the subjects stood with their backs against the gauge and feet on the weighing platform. All measurements were taken by the same person. CDC growth charts were used for boys and girls to assess their physical growth. Z-scores of height and weight were calculated. BMI was calculated as kg/m^2. According to WHO reference 2007, weight for age z-score <-2 SD is considered as underweight, and height for age z-score <-2 SD is considered as stunted. BMI expressed the nutritional status. Blood samples were taken by venipuncture from the cubital vein. Five ml of Venous blood sample was taken and put into a vacutainer clot activator tube and allowed to be kept at room temperature for 20 min. after that blood sample was centrifuged at 3000 rpm for 5 to 10 minutes and the serum was separated. Then Serum levels of ferritin were measured.

All statistical calculations were done using SPSS 22.0 for Windows (IBM SPSS Statistics. 22.0). Continuous variables are presented as mean standard deviation, and ordinal data are presented as count and percentage. ANOVA tests and unpaired t-tests were used for continuous variables. Pearson correlation coefficient was used to determine the correlation between BMI and serum ferritin level. P values <0.05 are considered statistically significant.

Results

The mean age was 10.62±3.74 years varied from 5 to 18 years. Male and female were found 32(47.8%) and 35(52.2%) respectively. Primary education was found 62(92.5%). Regarding the socio-economic status, 35(52.2%) belonged to the lower economic class, 30(44.8%) in the lower middle economic class and 2(3.0%) in the upper-middle economic class.

Figure 1 showed among the children with transfusion-dependent thalassemia 61% (n=41) patients were E-beta thalassemia and 39% (n=26) were beta-thalassemia major.

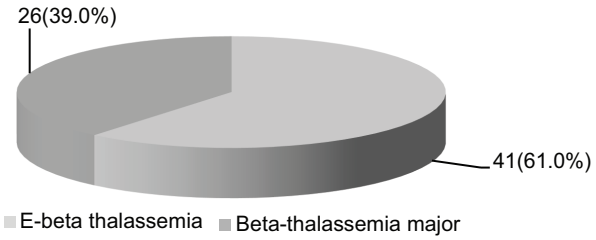

Fig.-1 *Distribution of Transfusion dependent Thalassemia according to type (N=67)*

Table I

Serum Ferritin status of children with Transfusion Dependent Thalassemia (N=67)

Characteristics	β-Thalassemia major (n=26) Mean±SD	E β-Thalassemia (n=41) Mean±SD	p-value
S. Ferritin	819.04±1085.48	2913.44±1304.53	0.750^{ns}

p-value reached from the unpaired t-test, ns=not significant

There was no significant difference in S. ferritin level between β-Thalassemia major group and E β-Thalassemia group (p=0.750) (Table I).

Table II showed distribution of height and weight of children with transfusion dependent thalassemia. Results are expressed as Mean ± SD.

Table II

Distribution of study samples by anthropometric data (N=67)

Characteristics	Mean ± SD	Range
Weight (kg)	25.48 ± 10.56	9.0-54.0
Height (cm)	130.15 ± 20.71	85.0-175

Table III showed, Weight for age Z (WAZ) score in the TDT group revealed 44.7% of children had under-weight. Height for Age Z (HAZ) Score showed 40.3% of children with transfusion dependent thalassemia had stunted growth. But there was no significant association between WAZ and HAZ with serum ferritin level.

Table III

Association between WAZ and HAZ with serum ferritin level (N=67)

Characteristics	S. ferritin		Range		p-value
	No.(%)	Mean±SD	Min	Max	
WAZ score					
Normal >-2	37(55.3)	2807.0±1271.9	851	6345	0.843^{ns}
Underweight <-2	08(11.9)	2995.7±987.00	900	4600	
Severely under-weight <-3	22(32.8)	3000.0±1504.7	900	5500	
HAZ score					
Normal >-2	40(59.7)	2889.34±1209.2	1100	6345	0.986^{ns}
Stunted <-2	15(22.4)	2836.73±955.00	851	4000	
Severely Stunted <-3	12(17.9)	2908.33±1415.2	900	5500	

p-value reached from ANOVA test, ns = not significant

Table IV
Association between BMI with serum ferritin level (N=67)

BMI	S. ferritin		Range		p-value
	No. (%)	Mean±SD	Min	max	
<5th percentile	33(49.3%)	3115.2±1028.7	900	5500	0.104ns
5th to 85th percentile	34(50.7%)	2638.9±1287.6	851	6345	

P value reached from the unpaired t-test, ns=not significant

Table IV showed 49.3% of children in the transfusion-dependent thalassemia group had BMI below 5th percentile. There was no significant association between BMI with serum ferritin level.

Figure 2 showed Scatter plot for correlation between BMI and Serum ferritin. There was negative non-significant correlation (r=-0.073; p=0.561) present between BMI and Serum ferritin.

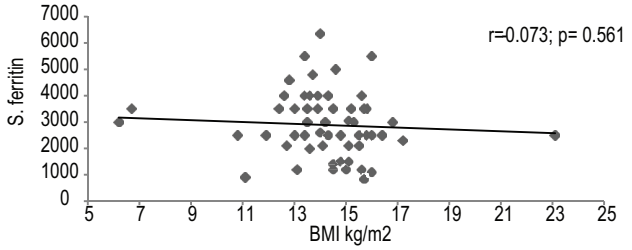

Fig.-2 *Scatter diagram between BMI with S. ferritin*

Discussion

Thalassemia is one of the most common hematological problems in clinical practice. Beta thalassemia major and E-beta thalassemia constitute a majority of the portion of thalassemia syndrome that needs to be treated. Patients with thalassemia have a poor growth spurt and multiple endocrinopathies. This study was conducted to assess growth parameters in children with transfusion-dependent thalassemia and their correlation with serum ferritin levels.

In this study, regarding the socio-demographic characteristics of the study children, it was observed that the mean age was 10.62±3.74 years varying from 5 to 18 years. More than half which is 35(52.2%) of the study children were female. Primary education was found in 62(92.5%), pre-primary found in 3(4.5%) and 2(3.0%) had secondary education level. Regarding the socio-economic status, 35(52.2%) belonged to the lower socio-economic class, 30(44.8%) to the lower middle socioeconomic class, and 2(3.0%) to the upper-middle socioeconomic class. One study reported that among a total of 25 children with an age range of 4-11 years, the mean age was 6.02 years with 12 males and 13 females.[11] Diab et al[12] observed that the patient group included forty thalassemic patients with a mean age of 11±2.86 years varied from 8-16 years. Hongally et al[13] reported that the mean age of the children was 7 years. Another study reported that females and males comprised 56.1% and 43.9% respectively.[14] In agreement with the present study, Thiyagarajan et al[15] concluded that family well-being is the foundation for the quality of life of children. It was found that factors such as family income and parents have a direct association with the Health-related quality of life (HRQoL) of children with thalassemia. Hongally et al[13] reported that 29 (58%) belonged to low socioeconomic status 25 (50%) were from rural origin 21 (42%) had income less than 3000 Indian Rupee (INR).

According to this study, 39% and 61% of patients had beta-thalassemia and E-beta thalassemia respectively. Olivieri et al[16] reported that worldwide, patients with hemoglobin E-beta-thalassaemia (Hb E/β-thalassaemia) represent approximately 50.0% of those affected with severe beta-thalassemia. The highest frequencies are observed in India, Bangladesh, and throughout Southeast Asia, particularly in Thailand, Laos, and Cambodia, where it is common for individuals to inherit alleles for both hemoglobin E (Hb E) and beta-thalassemia.[16,17] In southern China, due to gene frequencies of about 4.0% for β-thalassemia and Hb E, thousands of patients are affected. Hb E/β-thalassaemia is also common in Indonesia and Sri Lanka, and while previously rarely diagnosed in North America or Europe, has recently become the most common form of β–thalassemia identified by many newborn screening programs.[18] One study reported that in severe E-beta thalassemia, the Hb level can be as

low as 4-5 g/dl. Patients in this group manifest symptoms similar to thalassemia major and are treated as thalassemia major patients.[19]

This study reveals serum ferritin level was almost similar (2819.04±1085.48µg/l vs 2913.44±1304.53µg/l) between the beta-thalassemia and E-beta thalassemia group, no significant (p>0.05) difference was found between the two groups. Similarly, Vogiatziet et al [20] reported comparable ferritin levels from beta-thalassemia patients and E-beta thalassemia patients.

The weight for age Z (WAZ) score revealed that 44.7% of patients with transfusion-dependent thalassemia were underweight, out of which 32.8% were severely underweight and 55.3% of patients with transfusion-dependent thalassemia had normal weight. Nearly one-fourth (22.4%) had stunting and 17.9% had severe stunting in these transfusion-dependent thalassemia patients. In India, 65.71% of thalassemic patients were reported to have short stature and 77% were underweight.[21] Fahim et al[22] reported that 49.0% of their patients had a HAZ score <-2, and 47.0% of patients had a WAZ score <-2, which is similar to the present study. Regarding the association, it was observed that the mean Serum ferritin level was almost identical among different WAZ score and HAZ score categories, no significant (p>0.05) associations were found among the different WAZ score and HAZ score categories.

In this study, it was observed that almost half (49.3%) of the patients had a BMI less than the 5th percentile. The pathogenesis of growth failure in TDT patients is multifactorial and one of the main factors is iron overload.[1,7] Other contributing factors are chronic hypoxia, hormonal status, nutritional deficiency, endocrinopathies, and degree of iron-chelating agent utilization.[7] Similarly, like the WAZ score and HAZ score, it was also observed that there is no significant (p>0.05) relationship between Serum ferritin with BMI percentile. There is also no correlation (r=-0.073, p=0.561) between S. ferritin with BMI percentile.

Bulgurcu et al[23] reported that the mean Serum ferritin level was 1044.7±536.2 ng/mL in BMI <5th percentile, 1204.8±567.6ng/mL in BMI 5-50th percentile, 1230.5±677.4ng/mL in BMI 50-95th percentile and showed no significant differences in the mean serum ferritin with BMI percentile. The investigators also reported that anthropometric percentiles did not significantly differ in the mean serum ferritin levels, which supports the present study. Similarly, in another study, researchers reported no significant association between children's growth and serum ferritin levels.[24] However many other studies showed a significant association between serum ferritin levels with growth parameters in children with transfusion-dependent thalassemia.[1,21,25,26] Unlike previous studies, this study did not find any significant association between serum ferritin levels and growth parameters in our subjects. This can occur because growth depends on multiple factors and the mean level of serum ferritin also depends on multiple factors such as age at diagnosis, age of starting treatment, chelation therapy, and compliance to chelation.

Conclusion

This study showed that children with transfusion-dependent thalassemia had delayed growth and nearly half of the children were underweight and stunted. The mean serum ferritin levels are not associated with the growth parameters in transfusion-dependent thalassemia.

Limitations

This study has some limitations including a small sample size, only one center study, short duration of the study period as well as COVID-19 situation adversely affected the admission of patients to the hospital

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