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Association of Body mass index and serum ferritin level in pediatrics with Beta-thalassemia major disease

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Abstract

Background: Beta-thalassemia major is a type of inherited blood disease that results in variable outcomes such as severe anemia due to haemoglobin chains. Recurrent and lifelong blood transfusions as a treatment in beta-thalassemia major disease lead to iron deposition in various organs and cause the failure of multiple organs. Failure of affected organs leads to Body mass index (BMI) abnormality. This study aimed to evaluate the association between BMI and serum ferritin level as a marker for iron overload.

Materials and Methods: A cross-sectional study designed and conducted with total number of 740 paediatrics, with mean age about 14.2±8.7 years old and with beta-thalassemia major requiring recurrent blood transfusion. Patient information, including demographics, serum ferritin level and percentage of BMI, was recorded and analysed by SPSS 25.0 and the statistical significant level, considered as 0.05.

Results: A total number of 740 paediatrics with beta-thalassemia major disease (mean age about 14.2±8.7 years) were included to study to examine the association between serum ferritin level and their BMI. The total mean serum level of ferritin calculated about 3326 ± 3859 Nanogram/mililitter (ng/ml). Totally, 447 (60.4%) case of them had BMI percentile less than 5%, 274 (37.02%), 16 (2.16%) and 3 (0.4%) had BMI percentile 5%-85%, 85%-95% and more than 95%. There was no relation between gender and serum ferritin levels. The relationship between age and BMI has been positive (P=0.002). Finally, it resulted that there was a negative relationship between the BMI percentile and mean serum ferritin levels in paediatrics with beta-thalassemia major (P=0.031).

Conclusion: Frequent Blood transfusion is associated with elevated serum ferritin level in paediatrics with beta-thalassemia major disease and experiencing lower percentiles of BMI in these patients.

Keywords: Beta-thalassemia major, Blood transfusion, Body mass index, Ferritin, Iron overload**.**

Introduction

Beta thalassemia disease is a hereditary blood disorder, and about 3% of the population in the world carries its gene (1). This disease results in an abnormal form of hemoglobin production, molecular defects in the globin gene on chromosome 16 or 11 results in impaired hemoglobin synthesis (1), resulting in variable phenotypes ranging from severe anemic to clinically asymptomatic patients (2). There are three types of thalassemia based on the genetic form: beta-thalassemia, alpha thalassemia, and minor thalassemia. There are two subtypes of beta-thalassemia, major beta-thalassemia and intermediate beta-thalassemia. Beta thalassemia major has known to be the most severe form of beta-thalassemia, causing severe anemia (1). The treatment strategies for beta-thalassemia major includes:

- Frequent blood transfusion.
- Usage of antioxidant agents.
- Hematopoietic stem-cell transplantation to induction fetal hemoglobin in the patient.

However, the most common one to improve the patients' life expectancy is regular blood transfusion. It provides a base level of normal hemoglobin for patients but maybe still insufficient in these patients. Studies

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reported that about 100,000 patients with major thalassemia need a regular and lifelong transfusion every year (2). Regular blood transfusion could reduce complications due to anemia and provide the proper growth and development in pediatrics with thalassemia and their survival (2,3). Frequent blood transfusion can result in several side effects. As the human body's capacity and mechanisms for removing iron from the tissues are limited, in patients with regular blood transfusion, iron begins to be retained in the body, a condition known as an iron overload. It is a condition that can be fatal via causing toxic accumulation in cells of vital organs like the liver, pituitary gland, thyroid, pancreas, which correlates with a condition named hemochromatosis, an autosomal iron metabolism disease. It is characterized by increased iron uptake from the intestine) and transfusion-transmitted viral infections like hepatitis (1,2,4,). Regular red blood cell (RBC) transfusion and iron overload can cause endocrine abnormalities such as Hypogonadotropic hypogonadism, pituitary gland abnormalities, growth hormone deficiencies, and hypothyroidism (4). Also, poor sexual development and pubertal growth problems are seen in thalassemia patients who received regular blood transfusions (4,5,6). Iron overload causes serious issues such as organ failure caused by excess iron accumulating in tissues and organs and making organs dysfunctional. Patients' impaired growth, such as short stature and inadequate body mass index (BMI), may result from these conditions (7).

Some studies were conducted worldwide to evaluate the obtained results of frequent blood transfusion in beta-thalassemia major patients; however, the current study included a more extended study duration and a larger population to receive more definite treatment outcomes.

As it is necessary to enhance treatment protocols such as lifelong blood transfusion to achieve a better patient outcome, the present study was designed to evaluate the association of BMI and iron overload in patients with a beta-thalassemia major disease.

The presented background hypothesized that frequent blood transfusion is related to iron overload, and beta-thalassemia major can affect body organs and impair growth and lower BMI. Therefore, the present study was designed to evaluate the association of frequent blood transfusion and lower BMI in pediatrics with a beta-thalassemia major disease, admitted in Ali-Asghar university hospital, Zahedan, Iran.

Materials and Methods

Design and study sample

The present study is cross-sectional research conducted in patients with beta-thalassemia major. They received a recurrent blood transfusion as their therapeutic plan, from 2017/12/3 to 2018/12/3, in a total number of 740 patients admitted to the Ali-Asghar university Hospital of Zahedan University of Medical Sciences Zahedan, Iran.

Definitions and inclusion criteria

All beta-thalassemia major patients admitted to the Ali-Asghar university hospital for blood transfusion, included in our study. Exclusion criteria were other situations causing BMI changes, including underlying kidney disease, severe malnutrition or history of feeding intolerance, and early bone disorders. Patients with such conditions were excluded from the study. Patient information, including age, gender, weight, height, serum ferritin level, and BMI percentile, was recorded with filling questionnaire forms. Serum ferritin levels and the percentage of BMI in patients were measured in the hospital at the beginning of their admission. Of all, 405 patients (54.7%) were using iron chelators, 229 patients (72.9%) had less than ten years old, and 176(41.3%) had more than ten years old. Only 14 patients have not used any iron chelators, nine patients were less than ten years old, and five patients were more than

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ten years old. PISHTAZ TEB ZAMAN kit for ELISA kit and method were used to check the patient's serum ferritin level, and for measurement, the Nanogram/mililitter (ng/ml) unit was used.

BMI Measurement

The patient's height and weight were measured with a calibrated scale in the hospital examination room. The BMI was calculated based on the weight (kilogram)/ height (meter^2) formula. The BMI Percentile Calculator for children and adolescents" Center for Disease Control and Prevention (CDC)" was utilized to calculate the percentiles of BMI.

Statistical analysis

A descriptive and inferential method for statistical analysis was used on the data entered in SPSS 25(SPSS Inc., Chicago, USA)(20). Inferential statistical analysis was performed in two univariate and multivariate approaches. In the univariate approach, statistical tests such as chi-square test and independent t-test, nonparametric test (Mann-Whitney), and ANOVA were used if necessary. Quantitative variables were calculated, and results were expressed as mean ± SD. The statistically significant level was considered <0.05.

Ethical considerations

The present study was extracted from a medical student thesis (No. 2) and was submitted and approved by the deputy of research and technology, Zahedan university of medical sciences, Zahedan, Iran. All study ethical considerations were registered and approved by the research ethics committee of Zahedan University of medical sciences (ethical ID: IR.ZAUMS.REC.1396.130). The parents of eligible patients were informed of the study goals, and possible effects signed an informed consent form and assured of personal information's confidentiality. Treatment protocols for this study were not modified, and all patients were under treatment according to the treating physician's diagnosis. Patients' verbal informed consent for anonymous use of their medical data was obtained.

Results

A total number of 740 pediatrics with beta-thalassemia major were included in the present study, of which 380 (51.35%) were boys, and the rest were girls. The mean age of patients was 14.2±8.7 years (Table I). Total mean serum level among all patients of ferritin was 3326 ± 3859 nanogram/mililitter (ng/ml) and in males and females were 3810±3361 and 3910±3293 ng/ml, respectively. There was no significant relationship between serum ferritin level and gender (p = 0.450) (Table II). Patients BMI percentile was as follows: 447 (60.4%) of them had BMI percentile less than 5%, 274 (37.02%), 16(2.16%) and 3(0.4%) had BMI percentile 5%-85%, 85%-95% and more than 95%. Underweight (BMI <5%) was 287 (64.2%), 160 (35.8%) and Normal BMI (BMI=5%-85%) was 24 (8.8%) and 250 (91.2%) in less (L group) and more than 10 years old patients (M group), respectively. A positive association between patients' age and BMI, found in results (p=0.002). Also, 246 (55.0%) and 201 (35%) of males and females were Underweight. In patients with normal BMI, these frequencies were 101 (36.9%) and 173 (63.1%), respectively. There was no significant relationship between gender and BMI (p=0.89) (Table III). A negative relation between BMI percentile and mean serum ferritin level of patients found, as showed in table VI.

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Table I: descriptive statistics

	Total number	Gender		Mean age
		Male	Female	
Patients	740	380	360	14.2±8.7

Table II: serum ferritin level and gender

	Male	**Female**	**p-value**
Mean serum ferritin level(ng/ml)	3810±3361	3910±3293	0.450*

* ng/ml , is abbreviation for Nano gram per a mililitter, p-value=0.05

Table III:- Patients BMI percentile

	BMI percentile								**p-value**
	%5>		5-85%		85-95%		95%<		
total	447 (60.4%)		274 (37.02%)		16(2.16%)		3(0.4%)		
age group	L	M	L	M	-	-	-	-	0.002*
	287 (64.2%)	160 (35.8%)	24 (8.8%)	250 (91.2%)					
gender	male	female	male	female	-	-	-	-	p=0.89*
	246 (55.0%)	201 (35%)	101 (36.9%)	173 (63.1%)					

*BMI is abbreviation for body-mass index, L is abbreviation for less, M is abbreviation for more, p-value<0.05

Table VI: Percentile BMI and Mean serum level of ferritin

BMI Percentile	**Mean serum level of ferritin**	**Standard division**	**-value**
5%>	4257	4017	0.031
5-85%	3891	3260	
85-95%	3764	3690	
95%<	3504	3378	

Discussion

In the present study, 740 beta-thalassemia major patients with both genders and 14.2±8.7 years old of age to evaluate the hypothesis of frequent blood transfusion effect on growth in these patients, especially on BMI changes. In comparison to previous studies, the present study was conducted on the more significant population to increase the reliability of reported findings. It was found that serum ferritin levels in these patients are higher than the same population with the normal condition, and this increase has no relation with age or gender. Still, after analyzing the results, there seems to be a negative relation between the mean ferritin level of serum and BMI, which means that higher ferritin levels correlate with lower BMI. Weight loss was a common finding in these patients, especially those less than ten years old. It means that lower ages could make patients more susceptible to lower BMI. Obesity was not common in these patients. There was no relationship between gender and BMI index. Also, it was found that in pediatrics with low BMI percentile, the mean serum ferritin level is higher than others.

All of the discussed points clearly show that without a plan for controlling increased ferritin and iron overload, as a side effect of

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treatment in beta-thalassemia major patients who receive a regular blood transfusion, it could increase the risk of morbidity and mortality via growth impairment and lower BMI percentile. Due to recent reports about morbidity and mortality in multi blood transfused paediatrics with Beta thalassemia major, researchers are investigating about replacement of blood transfusion, with novel treatment approaches such as cell therapy (19).

As iron overload is a leading cause of mortality in beta-thalassemia major patients, an appropriate medical team approach for regular follow-ups is required to detect early iron overload evidence in patients and reduce it.

There are previous studies with the aim to evaluating regular blood transfusion on growth and development state of beta-thalassemia pediatrics; however, to the best of our knowledge, there are no previous researches with the same study population and aim to evaluate the effect of regular blood transfusion on serum ferritin level and BMI, was conducted in Iran.

A similar study, Pemde et al. (6), reported that 100% of the 214 beta-thalassemia patients had high ferritin levels and the mean serum ferritin levels in their patients were 3113 ng/ml. Also, they believed that the mean levels of serum ferritin depend on multiple factors, including factors such as patients age at presentation, age at beginning treatment by regular RBC transfusion, age at starting iron chelation therapy, the efficacy of iron chelation drug, and its compliance by the patient, and the age group of the reported series of patients. Deena S. Eissa et al. (7) reported that serum iron, total iron-binding capacity (TIBC), and ferritin level are higher in beta-thalassemia pediatrics than in normal groups. This study included sixty thalassemia patients, thirty percent of them had low BMI, but no-one experienced overweight. Eighty-two percent of patients showed high serum ferritin levels (>1000 ng/ml). In this study, researchers concluded ferritin has no value as an indicator of growth retardation in pediatrics with betta-thalassemia major. They found patients with significantly low BMI above 12 years old, rather than the normal population. However, in less than 12 years old patients, these difference wasn't significant.

Obesity is not a common finding in beta-thalassemia patients; various causes are responsible for these conditions, including endocrinopathies (12). In the present study, most patients were underweight. But, these percentages were lower in other studies. For example, a study by Hashemi A et al. (2) showed that 18.6% of the total 70% BMI of a thalassemia patient major beta was less than 5%. In Pemde HK et al.'s (6) study, 11% of patients had BMI Z-score < -3, and none of the cases were known as obese.

A study was done by Fung EB et al. (8) and showed 142 iron overload patients, but the mean BMI was at the normal range in this group. Dey et al. (11) also reported the same result, opposite the presented study. They noted this might be due to multiple endocrinopathies, especially hypogonadism, malnutrition in these patients, and aging. More extended organ involvement in older patients made them more susceptible to losing weight.

In concordance with present research results, Dey P et al. (11) showed no significant difference between gender and BMI percentile.

In concordance with present research results, In Hashemi A, et al. (2), the mean of serum ferritin level was significantly higher in the pediatrics with lower BMI and different from patients with normal BMI percentile, statistically 2679± 1378 ng/ml and 2596± 1777 ng/ml, respectively.

Shalitin et al. (16), in their 16.3-year prolonged study on 39 patients, reported that higher levels of serum ferritin in the first decade of life and during puberty is a risk factor of short stature and hypogonadism, respectively, which emphasize the role of high serum ferritin level as an essential and independent risk

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factor of impaired growth in beta-thalassemia patient.

Furthermore, in a study by Bushra et al., researchers reported iron overload as a cause for delayed growth in children with beta- thalassemia major disease. In this study, patient's height and ferritin levels of serum had significant negative association (16).

However, in study by Lubis et al., researchers reported no significant association between all 56 children's growth and ferritin levels of serum. But they identified children's age at time of diagnosis as an important factor for experiencing short stature (17).

Conclusion

High serum ferritin level in pediatrics with beta-thalassemia major is associated with low BMI percentile due to regular therapeutic blood transfusion. Therefore, iron chelators should be considered in these patients as an option for treating iron overload as the main complication of recurrent blood transfusion and its related side effects such as various organ damage which increase patient's susceptibility to experience lower BMI percentiles in comparison to the same groups in age, with considering the impact of ethnic and socioeconomic factors.

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Conflict of interest

The authors declared no conflict of interest.

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