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Evaluation of malnutrition in transfusion-dependent children with beta-thalassemia major

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ABSTRACT

Objective: In patients with thalassemia, factors such as low socioeconomic status, rapid erythrocyte turnover, endocrinopathy, chronic hypoxia, increased nutritional demands, multiple transfusions, and ineffective erythropoiesis may lead to malnutrition. This study aimed to investigate malnutrition and related factors in children with transfusion-dependent beta-thalassemia major (β-TM).

Material and Methods: The research group consisted of the medical records of 81 β-TM patients. Data were created by measuring the patients height (cm), body weight (kg), weight for age, mid-upper arm circumference (MUAC, cm), triceps skinfold thickness (TSF, mm) and blood parameters (e.g., hemoglobin, ferritin) before transfusion.

Results: The median age of children with β-TM was 8.8 (range, 4.6-13.0) years, 38 (47%) were male and 43 (53%) were female. The frequency of malnutrition among the children was 20.99% (4.94% moderate, 16.05% mild). The median age of those with malnutrition was higher (p=0.003) and the frequency of malnutrition was higher in children with β-TM aged 5 years and over (p=0.034). Children with and without malnutrition were similar in terms of body weight (p=0.074), MUAC (p=0.321), MUAC z-score (p=0.573), TSF (p=0.691), TSF z-score (p=0.846), TSF percentile (p=0.077), ferritin (p=0.945), vitamin B12 (p=0.119), 25-OH Vit D (p=0.995), and hemoglobin (p=0.563). Body mass index (p=0.026) and weight for age (p<0.001) were lower and albumin was higher (p=0.041) in children with malnourishment.

Conclusion: Malnutrition in children with transfusion-dependent β-TM is still a common clinical picture that needs to be tackled and prevented.

Keywords: Beta-thalassemia child, child nutrition disorders, ferritins malnutrition, iron chelating agents

INTRODUCTION

B-thalassemia major (β-TM) is an autosomal recessive type of hereditary disease in which genetic mutations affect the β-globin gene, disrupting the synthesis of functional β-globin protein. In this disease, an imbalance between α- and β-globin chains and erythropoiesis damage occur (1). Erythropoiesis injury causes premature erythrocyte destruction and causes chronic anemia with extramedullary hematopoiesis and associated bone marrow enlargement (2).

Inherited hemoglobin disorders, including thalassemia, are the most common monogenic diseases worldwide (3). Globally, it is estimated that 300.000 to 400.000 babies are born with a severe hemoglobin disorder each year (23.000 with β-TM), and up to 90% of these births occur in low or middle-income countries. Although thalassemia is common, it is most common in sub-Saharan Africa, Southeast Asia, and the Mediterranean region (4,5). The prevalence of β-TM is higher in lower-middle-income countries (e.g., India, Pakistan, Iran, and Egypt), and is lower in high-middle and high-income countries (e.g., Türkiye, Greece, the United States of America, and Canada) (6). The prevalence of β-thalassemia carriage in Türkiye is 2.1% (0.6-13.0%) (7).

In many patients with β-TM, circulating nutrient levels are reduced due to increased requirements, increased excretion, and/or malnutrition (8). In patients with thalassemia, low

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socioeconomic status, rapid erythrocyte turnover, long-term use of iron chelation, endocrinopathy, hypoxia due to anemia, increased body demand for energy and nutrients, and multiple blood transfusions and ineffective erythropoiesis may complicate the normal development process and lead to malnutrition (9,10).

The study aimed to evaluate the frequency of malnutrition and related factors in patients with transfusion-dependent β-TM.

MATERIALS and METHODS

This retrospective study was conducted at Batman Training and Research Hospital between July 2021- December 2021.

Ethics committee approval of the study was obtained from local ethics committee. Due to retrospective design of study, it is not necessary and not possible to take informed consent from recruited patients.

The medical records of 81 β-TM patients in the pediatric hematology outpatient clinic for the time period in which the research was conducted constituted the research data. All of these patients were subjected to a regular transfusion program to keep hemoglobin levels under control. Erythrocyte suspensions are administered regularly to patients at intervals of 3-4 weeks. Before transfusion, height (cm), body weight (kg), weight for age, mid-upper arm circumference (MUAC, cm), triceps skinfold thickness (TSF, mm) and blood parameters (e.g. hemoglobin, ferritin) are measured and recorded.

While measuring body weight, the caregiver was asked to remove the children's outer clothing and shoes. The children were asked to stand still on the scales with their feet slightly apart and they were measured and recorded using a calibrated scale. For height measurement, the children were asked to take off their shoes and the distance between the point marked with a board placed perpendicular to the wall and the floor was recorded when they stood upright on a flat surface (11). Mid-upper arm circumference was measured in centimeters with a non-stretched, standardized measuring tape. For measurement, the right arm was hung loosely and the midpoint between the tip of the acromion and the olecranon protrusion was determined. At this determined point, the tape was placed around the arm, preventing the soft tissue from being too tight or too loose. Two different measurements were made at a distance closest to 0.1 cm (12). The anthropometric measurement values of the children were compared with the age-appropriate World Health Organization (WHO) growth charts, and it was evaluated whether there were any malnutrition features. Children were classified according to the presence of malnutrition as mild, moderate, severe, or absent. Weight-for-height z-score values below -3 SD were classified as severe malnutrition, between -3SD and -2SD as moderate malnutrition, and between -2SD and -1 SD as mild malnutrition (13,14).

Statistical analysis

All analyses were performed using the IBM SPSS Statistics for Windows, Version 25.0 software package (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to determine whether variables were normally distributed. Data are given as mean and standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. Continuous variables were analyzed using Student's t-test or the Mann-Whitney U test depending on the normality of distribution. Categorical variables were analyzed using the Chi-square test or the Fisher-Freeman-Halton test. Statistical significance was accepted as $p<0.050$.

RESULTS

The median age of the children in the study group was 8.8 (range, 4.6-13.0) years; 38 (47%) were male and 43 (53%) were female.

The frequency of children in the study group with body mass index (BMI) z-scores between -2 SD and -1 SD was found as 16.05%, those with BMI z scores between -1 SD and 0 SD were 46.91%, and the frequency of those with BMI z-scores between 0 SD and 1 SD was 27.16%. The prevalence of malnutrition among the children was 20.99% (4.94% moderate malnutrition, 16.05% mild malnutrition). Weight for age was determined as 28 (range, 10-44), MUAC 18 (range, 16-20) cm, TSF 9 (range, 7-11) mm. The frequency of MUAC, z-score (< 5 years) -3SD to -2SD was 7.4% and -2SD to -1SD was 29.63%. The frequency of TSF, z-score (<5 years) -3SD to -2SD was 18.52% and -2SD to -1SD was 22.22% (Table I).

Among the children with transfusion-dependent β-TM, the median age of children with mild-moderate malnutrition was significantly higher than those without malnutrition (p=0.003). The frequency of mild/moderate malnutrition was 7.42% in children aged younger than 5 years, and 27.78% in children aged 5 years and over. The frequency of mild/moderate malnutrition was higher in children aged 5 years and over with β-TM (p=0.034). Children with and without malnutrition were similar in terms of sex (p=0.098), body weight (p=0.074), MUAC (p=0.321), MUAC z-scores (p=0.573), TSF (p=0.691), TSF z-score (p=0.846), TSF percentile (p=0.077), ferritin (p=0.945), vitamin B12 (p=0.119), vitamin D (p=0.995), and hemoglobin (p=0.563). Height (p=0.004) was significantly higher in children with malnutrition, and BMI (p=0.026) and weight for age (p<0.001) were significantly lower. The median albumin level was found to be higher in children with malnutrition (p=0.041, Table II).

Table I: Summary of characteristics, and anthropometric and laboratory measurements	
Age (years)*	8.8 (4.6-13.0)
<5†	27 (33.33)
≥5†	54 (66.67)
Age (months)*	105.6 (55.2-156.0)
Gender†	
Male	38 (47)
Female	43 (53)
Weight (kg)*	25.5 (17-34)
Height (cm)	127 (107-143)
Body mass index (kg/m^2)*	16.06 (15.08-18.08)
Body mass index, z-score†	
-3SD to -2SD	4 (4.94)
-2SD to -1SD	13 (16.05)
-1SD to 0SD	38 (46.91)
0SD to 1SD	22 (27.16)
1SD to 2SD	4 (4.94)
2SD to 3SD	0 (0.00)
Malnutrition†	
Absent	64 (79.01)
Mild	13 (16.05)
Moderate	4 (4.94)
Severe	0 (0.00)
Weight for age*	28 (10-44)
MUAC (cm)*	18 (16-20)
MUAC, z score (<5 years)†	
-3SD to -2SD	2 (7.41)
-2SD to -1SD	8 (29.63)
-1SD to 0SD	7 (25.93)
0SD to 1SD	10 (37.04)
1SD to 2SD	0 (0.00)
2SD to 3SD	0 (0.00)
TSF (mm)*	9 (7-11)
TSF, z-score (<5 years)†	
-3SD to -2SD	5 (18.52)
-2SD to -1SD	6 (22.22)
-1SD to 0SD	5 (18.52)
0SD to 1SD	9 (33.33)
1SD to 2SD	2 (7.41)
2SD to 3SD	0 (0.00)
Albumin (g/dL)‡	4.51±0.28
Ferritin (ng/mL)*	1138 (816-1609)
Vitamin B12 (pg/mL)*	398 (310-651)
25-OH Vit D (ng/mL)*	12 (10.2-15)
Hemoglobin (g/dL) ‡	9.27±0.93

***:** *median (1st quartile-3rd quartile),* **†:** *n(%),* **‡:** *mean±SD,* ***MUAC:** Mid-upper arm circumference,* ***TSF:** Triceps skinfold thickness*

DISCUSSION

Generally, daily consumption of nutrients is significantly lower in children with β-TM, and anthropometric measurements recorded in children with β-TM are lower compared with healthy children (15). Malnutrition, as assessed using anthropometric measures, is quite common in children with thalassemia major (16). In previous reports, there is quite a wide range of results for the frequency of malnutrition in patients with β-TM, ranging from 24% to 70%. Based on the literature review, malnutrition prevalence among children with beta thalassemia major shows considerable variation across studies, with rates ranging from a low of 19.6% in girls in the Iranian cohort to a high of 70% in the Egyptian pediatric population, demonstrating significant geographic, methodological, and demographic differences in nutritional status assessment and outcomes (17-24) (Table III). In the current study, we found the frequency of mild-moderate malnutrition as 20.99% in children with β-TM. Possible differences in factors such as age, duration of treatment, dose of treatment, available treatment options, and criteria by which malnutrition was evaluated may explain the heterogeneity of outcomes. On the other hand, although the prevalence of malnutrition found in our study is lower than that reported in previous studies, our rate is not at the desired level. New methods are needed to reduce and prevent malnutrition, which is one of the important causes of morbidity and mortality in this patient group, and has many clinical disadvantages.

Malnutrition in children with thalassemia major increases with age, regardless of gender (16). In a study evaluating children with thalassemia major aged over 5 years, it was reported that BMI decreased in patients with thalassemia major aged over 10 years (70.4%) compared with patients aged younger than 10 years (30.4%) (25). In the study of Sheikh et al. (23), it was reported that the frequency of malnutrition increased with increasing age in children with β-TM between the ages of 2 and 16 years. In the study of Biswas et al. (22), although no relationship was found between gender and malnutrition in the multivariate analysis, it was reported that age increase was a factor that predicted the presence of malnutrition independently from other factors. Similarly, in the present study, the median age of children with β-TM who had mild-moderate malnutrition was higher, and no relationship was found between gender and malnutrition. The age of patients also indicates the disease and treatment duration because thalassemia emerges from birth. Over time, the negative effects of repeated transfusions and treatments on nutritional levels may increase. The nutritional status of patients should be monitored regularly and nutritional support should be provided when necessary.

Children with β-TM have lower hemoglobin levels than healthy children due to erythropoiesis damage and rapid cycling (26). In an observational study conducted with patients with β-TM, an increase in the number of transfusions performed in the last year and a decrease in hemoglobin levels before the last transfusion were reported as independent predictors of the presence of malnutrition (22). In the present study, the mean hemoglobin level before transfusion was lower than normal (9.27±0.93) and there was no correlation between malnutrition and hemoglobin levels. Due to the continuous decrease in hemoglobin in these patients, hemoglobin levels are closely monitored and regular transfusions are attempted to ensure control.

Table II: Summary of characteristics, and anthropometric and laboratory measurements according to malnutrition

	Malnutrition		p
	Absent (n=64)	Mild and Moderate (n=17)	
Age (years)*	7.6 (4.5-12.2)	13 (11.7-14)	0.003
<5 †	25 (39.06, 92.59)	2 (11.76, 7.41)	0.034
≥5 †	39 (60.94, 72.22)	15 (88.24, 27.78)	
Age (months)*	91.2 (54-146.4)	156 (140.4-168)	0.003
Gander †			
Male	27 (42.19)	11 (64.71)	0.098
Female	37 (57.81)	6 (35.29)	
Weight (kg)*	24 (16.85-34)	32 (28-35)	0.074
Height (cm)*	123.5 (105.5-138)	143 (137-147)	0.004
Body mass index (kg/m^2)*	16.26 (15.16-18.37)	15.65 (14.92-16.65)	0.026
Weight for age*	33 (16-51.5)	2 (1-5)	<0.001
MUAC (cm)*	17.5 (15.75-20.25)	18.5 (18.0-19.5)	0.321
MUAC, z-score (<5 years) †			
-3SD to -2SD	2 (8)	0 (0)	0.573
-2SD to -1SD	7 (28)	1 (50)	
-1SD to 0SD	6 (24)	1 (50.00)	
0SD to 1SD	10 (40)	0 (0)	
1SD to 2SD	0 (0)	0 (0)	
2SD to 3SD	0 (0)	0 (0)	
TSF (mm)*	9 (7-11)	8 (7-10)	0.691
TSF, z-score (<5 years) †			
-3SD to -2SD	5 (20)	0 (0)	0.846
-2SD to -1SD	6 (24)	0 (0)	
-1SD to 0SD	4 (16)	1 (50)	
0SD to 1SD	8 (32)	1 (50)	
1SD to 2SD	2 (8)	0 (0)	
2SD to 3SD	0 (0)	0 (0)	
Albumin (g/dL)‡	4.47±0.27	4.63±0.30	0.041
Ferritin (ng/mL)*	1126.5 (806.5-1619)	1150 (878-1519)	0.945
Vitamin B12 (pg/mL)*	413.5 (323.5-680.5)	318 (290-423)	0.119
25-OH Vit D (ng/mL)*	12.0 (10.1-15.2)	12.29 (11.0-14.9)	0.995
Hemoglobin (g/dL)‡	9.24±0.99	9.39±0.64	0.563

:** *median (1st quartile-3rd quartile) (Mann-Whitney U test),* **†:** *n(%) (Pearson Chi-square test),* **‡:** *mean±SD (Student's t-test),* ***MUAC: *Mid-upper arm circumference,* ***TSF:*** *Triceps skinfold thickness,* ***Note:*** *First percentage for age in parentheses represents within-group frequency; second percentage reflects proportion in total malnutrition category.*

Table III: Summary of reported malnutrition prevalence and assessment methods in pediatric β-thalassemia major studies

Study	Country	Year	Sample Size	Age Range	Malnutrition Prevalence (%)	Measurement Criteria
Qaisar et al. (16)	Pakistan	2020	300	0-215 months	45% (0-59 months) 67.5% (60-215 months)	WHO BMI classification
Pemde et al.(18)	India	2011	154	0.5-18 yrs	24.19	BMI for age
Trehan et al. (19)	India	2015	964	0-2 yrs	26.7	Weight for age
Mirhosseini et al. (20)	Iran	2013	140	8–18 yrs	44.3 % for boys 19.6 % for girls	WHO-BMI
Fahim et al. (21)	Egypt	2013	100	N/ A	47.0	Weight for age
Biswas et al. (22)	India	2021	328	5–12 yrs	48.2	WHO-BMI
Sheikh et al. (23)	Pakistan	2017	305	2–16 yrs	58.69	CDC-BMI
Mahmoud et al. (24)	Egypt	2021	120	≤12 yrs	70.0	WHO Z-score (BMI-for-age)

Thalassemia major increases long-term extravascular hemolysis and, as a result, intestinal iron absorption. When the iron overload that comes with multiple blood transfusions is added, the amount of iron in the tissue may exceed normal limits. Excessive iron accumulation is important because it can produce hydroxyl free radicals and oxidative stress, causing progressive tissue damage in the liver, heart, endocrine glands, and other organs. Controlling serum ferritin levels with combined iron-chelating agents has been associated with a decrease in the prevalence of endocrine disorders in patients with transfusion-dependent β-TM (24,27). According to a study in mice, iron overload causes MIN6 cell dysfunction, which leads to increased fasting blood sugar, impaired glucose tolerance, and significantly reduced insulin sensitivity (28). It has been reported that the prevalence of cardiac iron overload and cardiovascular complications is high in patients with thalassemia major (29). Serum ferritin levels are higher in patients with β-TM compared with healthy children (26). In another study conducted with children with β-TM, it was reported that the mean serum ferritin level was 3326±3859 ng/mL and there was a negative correlation between the BMI percentile and mean serum ferritin levels (30). In the study of Işık et al. (31), the mean ferritin levels of patients with β-TM were reported as 2497±1469 (range, 472-8558) ng/mL (31). In a study evaluating 367 children aged 5-17 years with transfusion-dependent β-TM, it was reported that serum ferritin value was 5012 (range, 3532-6829) ng/mL, higher than normal values (32). In another study, it was reported that the median serum ferritin value in patients with β-TM was 1365 (range, 362-5996) ng/mL, and no relationship was found between ferritin levels and anthropometric measurements (33). In the present study, the median ferritin value was 1138 (range, 816-1609) ng/mL, higher than normal values, in patients with β-TM, and additionally, no relationship was found between malnutrition and ferritin. Although the ferritin value found in our study group is lower than those reported in other studies, it is above the values considered normal for ferritin. To ensure that ferritin, which is one of the leading causes of morbidity and mortality in patients with β-TM, remains within normal values in this patient group, we need new ideas about non-transfusion treatments of the disease or the effectiveness of iron chelation treatments in patients undergoing transfusions. On the other hand, insufficient compliance, which is common in current iron chelation treatments, should be taken into consideration and controls should be provided to ensure treatment compliance of patients. Higher compliance is associated with lower serum ferritin, lower risk of complications, and better quality of life (34).

Disturbances between intake and circulating nutrient levels are observed in patients with β-TM, despite apparently adequate dietary intake, for reasons such as decreased nutrient absorption, increased loss, and increased needs due to increased nutrient cycling (6,10,35). Although 25-OH Vit D deficiency is a common comorbidity in patients with thalassemia, both its prevalence and severity vary considerably in different populations (36). In the study of Fahim et al. (21), it was reported that total serum calcium and 25-OH Vit D values of patients with β-TM were significantly lower compared with healthy controls. In the study of Altıncık et al. (33), the frequency of 25-OH Vit D deficiency in patients with β-TM was reported as 54.5%, and 78.2% in the study of Işık et al. (31). In a study conducted with adult patients, it was reported that the prevalence of low 25-OH Vit D was 92.2%, and no relationship was found between malnutrition and 25-OH Vit D levels (17). Similarly, in the current study, the 25-OH Vit D level was lower than normal values and was not associated with malnutrition. Both malnutrition and 25-OH Vit D deficiency are a result of β-TM. Children with β-TM should be followed closely in terms of 25-OH Vit D levels, especially in winter, and supplements should be provided in case of deficiency.

Treatment and follow-up of β-TM with a multidisciplinary approach will be beneficial because it has the potential to cause multisystemic complications (31). Periodic close monitoring of nutritional status is needed to determine the risk of malnutrition in patients with thalassemia (37). Although the issue of nutrition is increasingly seen by caregivers for patients with thalassemia, the definition of optimal nutritional support and the means of providing this support are still unclear and need to be studied (38).

The study had some limitations. This was a retrospective single-center study that failed to establish a causal relationship between malnutrition and some factors in children with β-TM. In addition, it was performed with a small number of patients. For these reasons, the statistical significance of some relationships may have been lost and the results cannot be generalized to the general population. Another limitation is that it does not have a healthy age- and sex-matched control group. The lack of analysis of data on patients' dietary regimens is another important limitation of this study. A further limitation is the possibility of other factors affecting malnutrition that were not evaluated in the study. Despite these, this study is valuable in terms of evaluating the relationship between malnutrition and many parameters in children with β-TM.

CONCLUSION

Malnutrition in children with transfusion-dependent β-TM is still a common clinical picture that needs to be tackled and prevented. It would be useful to monitor these patients closely in terms of iron accumulation and nutritional deficiency. More comprehensive, population-based, prospective studies are needed to better understand nutritional deficiency in patients with β-TM.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. Ethics committee approval of the study was obtained from Batman Training and Research Hospital Ethics Committee (Decision date: 25.07.2023, decision no: 358).

Contribution of the authors

Çakmakçı S: Concept, Design, Data Collection and Processing, Analysis and Interpretation, Literature Review, Writing the Article, Critical Review, Supervision. ***Danış KG:*** Design, Data Collection and Processing, Literature Review, Critical Review, References and Fundings, Materials. ***Tunç F:*** Supervision, Data Collection and Processing, Analysis and Interpretation, Literature Review, Critical Review, References and Fundings. ***Sarı N:*** Supervision, Analysis and Interpretation, Writing the Article, Critical Review, Materials.

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Conflict of interest

The authors declare that there is no conflict of interest.

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