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Association of Body Composition and Biochemical Indicators with Serum Ferritin Levels in Patients with β-thalassemia Major: A Cross-Sectional Study

Cirruse Salehnasab PhD[1], Farzad Karimpour PhD[2], Elaheh Piraei PhD candidate[3], Behrooz EbrahimzadehKour PhD[3, 4*]

1. Social Determinants of Health Research Center, Yasuj University of Medical Sciences, Yasuj, Iran
2. Shahid Beheshti Hospital Clinical Research center, Yasuj University of Medical Sciences, Yasuj, Iran
3. Student Research Committee, Yasuj University of Medical Sciences, Yasuj, Iran
4. School of Health and Nutrition Science, Yasuj University of Medical Sciences, Yasuj, Iran

*Corresponding author: Dr. Behrooz Ebrahimzadeh Kour, Student Research Committee, Yasuj University of Medical Sciences, Yasuj, Iran,Yasuj University of Medical Sciences, Yasuj, Iran. Email: ebrahimzadeh1358@gmail.com. ORCID ID: 0000-0003-0506-564X.

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Abstract

Background: This study aimed to assess the body composition and biochemical markers of patients with β-thalassemia major (BTM) in relation to their serum ferritin levels.

Materials and Methods: In this cross-sectional study, 74 BTM patients referred to an educational hospital in the southwest of Iran. They were grouped based on their serum ferritin levels. Given the cutoff point of 1500 ng/mL, 34 patients with acceptable serum ferritin level while 40 with high serum ferritin level. Anthropometric and biochemical indicators were collected following standard protocols. Dietary intake and body composition were evaluated by a 24-hour food recall and bioelectrical impedance analysis (BIA), respectively. The predictors of the serum ferritin level were determined by multivariate binary logistic regression, with the significance set at $P < 0.05$.

Results: Of the BTM patients, 16 (21.6%), 51 (68.9%) and 7 (9.5) were underweight, normal weight and overweight, respectively and no one them were obese. The daily intakes of vitamin K, vitamin D, vitamin B6 and copper were different significantly between two groups ($P < 0.05$). The mean blood transfusion interval was longer in acceptable ferritin level group compared to high ferritin group ($P = 0.04$). Fatness ($P = 0.02$) and total body water to lean body mass ratio (TBW/LBM) ($P = 0.047$) differed significantly between two groups. In fully adjusted regression model, the participants in the upper median group of fatness showed 81% lower odds ratio(OR) for high serum ferritin level (OR: 0.19, %95 confidence interval(CI): 0.033-0.84, $P = 0.03$). The association between TBW/LBM and serum ferritin level was positive, but not statistically significant in the fully adjusted model (OR: 3.66; 95% CI: 0.8–16.7; $P = 0.096$).

Conclusion: High body fat percent (BFP) is significantly associated with the lower odds of high ferritin levels, suggesting a potential protective role in BTM patients.

Keywords: Body composition, Ferritin, Growth, Iron overload, Thalassemia Major

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Introduction

In β-thalassemia major (BTM), a globally prevalent autosomal recessive monogenic disorder (1), deficient synthesis of hemoglobin chains, and ineffective erythropoiesis, lead to severe anemia (2). As a result, these patients depend on blood transfusion and chelation therapy for survival (3). More than one-twentieth of the world's population carries the gene for it (4), and nearly 60,000 new cases are identified each year (5). Although bone marrow transplantation is a potential cure, its implementation is often restricted due to adverse effects and a high mortality rate associated with the procedure (6). The primary treatment for BTM patients involves frequent blood transfusions, which is crucial for preventing death due to severe anemia and associated hematopoietic complications. However, the amount of iron that may be absorbed through food over several years can enter the body in just one session of blood transfusion. Iron accumulation can cause serious damage to vital organs such as heart and endocrine glands, ultimately leading to heart attacks, which account for three-quarters of premature deaths in these patients (7, 8).

Iron chelators play a pivotal role in preventing iron toxicity by effectively removing the excess iron and neutralizing the free iron in cells (9). The impact of BTM on patients' health encompasses a spectrum of challenges. Red blood cell hemolysis, oxidative stress caused by iron accumulation, increased excretion, and insufficient nutritional intake lead to a decrease in growth hormone secretion, growth failure, and bone problems (10). Of course, food sources of iron have valuable nutrients such as zinc and essential amino acids for the body. So, restricting such food sources causes a lack of other nutrients (11). BTM patients frequently experience problems such as pain, uncomfortable feelings in treatment procedures, low self-confidence, fear of premature death, and absenteeism from school or work (12, 13). Physiological disorders, insufficient food intake, and reduced physical activity due to bone problems can even cause the abnormality of body composition in these patients (14-16). Many of BTM patients experience short stature and hypogonadism.

Additionally, despite receiving adequate food, these patients exhibit low serum levels of vitamins and minerals. This suggests that their nutrient needs may be increased due to factors such as poor absorption, heightened excretion, or rapid turnover of nutrients. Malnutrition among these patients varies across countries, with lower-middle-income nations exhibiting higher prevalence compared to higher-middle and high-income countries (17-21). Given that the examination of body composition in these patients has received inadequate attention, this study seeks to fill part of the gap by evaluating the body composition and growth indicators of BTM patients in relation to their serum ferritin levels.

Material and Methods

Patients and research protocol

First, the executive protocol of this cross-sectional study was reviewed and approved by the ethics committee of Yasuj University of Medical Sciences (Ethical code: IR.YUMS.REC: 1396.25). Then, using the convenience sampling method, 74 BTM patients with minimally six months of blood transfusion were selected. Signed informed consent was obtained from all the participants before recruitment for the study. Parental signed consent was also obtained in the case of the patients under 18 years of age. The exclusion criteria were steroid therapy and the use of any drug affecting the body composition (19). According the serum ferritin threshold level of 1500 ng/mL (23), the BTM patients were defined as a group with an acceptable serum ferritin level (n = 34) and a group with a high serum ferritin level (n = 40).

Anthropometric and nutritional measurement

The weight and height of the BTM patients were measured using a standard measuring scale (Seca, Germany). The body mass index (BMI) was calculated as weight (kg) divided by squared height (m2). In the patients older than 20, the underweight, normal weight, overweight and obesity were determined based on the BMI values; In the patients under 20 years of age, the corresponding percentiles of the Center of Disease Control (CDC) charts were taken into account. CDC percentiles were also used to determine the height growth of the patients (2). Blood pressure

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was measured after overnight fasting and in standard conditions in the morning before any physical activity, smoking, and intake of coffee or any other stimulant drinks with standard Blood pressure monitor (DDM, Inc. Castelculier, France). For the adolescents > 12 yearsold, hypertension was defined as systolic blood pressure (SBP) > 120 mm Hg and diastolic blood pressure (DBP) > 80 mmHg. In the patients aged less than 12 years, hypertension was defined to be ≥ 90th of gender-matched blood pressure (24). Daily food intake was recorded using a 24-hour recall questionnaire during interviews with the patients, and the data were extracted using the NUT.4 software.

Body composition measurement

The body composition was analyzed through the bioelectrical impedance analysis (BIA) method (Body Composition Analyzer, ZEUS 9.9 PLUS, Korea). In this method, a very low electrical current (800 µA, 50 kHz) is transmitted through the body, and the impedance across different body segments is measured. It is based on a non-invasive bioelectrical resistance analysis to gauge body composition. Prior studies have confirmed the accuracy and reliability of body composition estimations derived from this method (25). Its efficacy has been confirmed particularly when dual-energy x-ray absorptiometry (DXA) is unavailable (26). For precise measurements, the patients were required to remove all metal items such as watches, belts and jewelry from their bodies. Additionally, trained technician conducted the measurements using a standardized protocol. This standardized approach helped maintain consistency and accuracy across the measurements. The rate of fat in different parts of the body, the non-fat tissues, and the water and minerals in the body were recorded with unique codes for each patient.

Biochemical measurement

To measure the blood parameters, venous blood samples were collected from the participants after a 12-hour overnight fasting period. The blood samples were then centrifuged at 3000 rpm for 20 minutes to extract the serum. The serum was subsequently isolated, and then the blood indices were measured using laboratory kits (Tehran Biochemistry) with a BT-3500, 3000 device (Bio Technica Company, Italy). For children and adolescents, the acceptable, borderline and high levels of total cholesterol (TC) were classified based on TC < 170, 170-190 and > 200 mg/dl, respectively, or drug therapy for dyslipidemia. However, high-density lipoprotein-cholesterol (HDL-C) levels were identified to be > 45 mg/dl or > 10th percentile, 40-45 mg/dl and < 40 mg/dl or < 10th percentile, respectively. In adults, the ranges for TC were < 200, 200-240 and > 240 mg/dl, respectively, or drug therapy for dyslipidemia. The normal HDL-C level was defined as ≥ 40 mg/dl in males and ≥ 50 mg/dl in females (27). The diagnosis of diabetes was based on fasting blood sugar (FBS) ≥ 126 mg/dl or drug or insulin therapy for diabetes.

Statistical analysis

The quantitative data were expressed as mean ± standard (M ± SD) and the qualitative data as number (n or %). The data distribution was determined by the Kolmogorov-Smirnov test through the Statistical Package for Social Sciences (SPSS, Version 26) software. One-sample t-test and independent samples t-test were used to analyze the parametric data, and Wilcoxon test and Mann-Whitney U tests for the nonparametric data. The difference of the categorical variables between the two groups of patients was also analyzed using chi-square test. Moreover, the significant characteristics affecting the serum ferritin level were identified using a crude model (Model 1) and the adjusted models of binary logistic regression. In primary adjustment (Model 2), age, gender and BMI were considered as the confounder variables. In the full adjustment model (Model 3), additional adjustments were done for the HDL-C level, transfused blood volume, interval between the transfusion sessions, and daily energy intake through determining the odds ratios (OR) and 95% confidence intervals (CI). A P-value of < 0.05 was considered as the significance level.

Results

The general characteristics of the BTM patients, including anthropometric, social and biochemical variables are reported in Table I. The data analysis showed that the chronological age (P = 0.25), physiological age (P = 0.94), and age at the disease

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diagnosis time (P = 0.33) did not differ significantly between the two groups. However, in the group with an acceptable serum ferritin level, the disease was diagnosed at a younger age than in the high-ferritin group. The volume of blood transfused in each treatment session was not significantly different between the two groups, although it was slightly lower in the group with acceptable ferritin levels (P = 0.39). Notably, the time interval between the blood transfusion sessions was significantly longer in the first group than in the second group (P = 0.04). In the first group, 11.8%, 82.3%, and 5.9% of the patients were underweight, normal weight and overweight, respectively. In the second group, however, these values were 30%, 57.5%, and 12.5%, respectively. The differences in weight categories between the two groups were not significant statistically (P = 0.07). Among the patients under 20 years of age, 38.5% in the first group and 44.4% in the second group were stunted. This difference was not significant (P = 0.83). The prevalence of diabetes was 11.8% and 10% in the first and second groups, respectively, but the difference was not significant (P = 0.81). In our study, 50% and 65% of the patients respectively in the first and second groups had low hemoglobin levels, with no significant difference (P = 0.19). For low HDL-C levels, the corresponding percentages were 70.6% and 87.5% (P = 0.07). None of the patients in either group had a high serum cholesterol level. Only 2.9% of the patients and only in the first group had high blood pressure.

According to Table II, the body fat percentage (BFP) was not significantly different between the two groups (P = 0.57); however, it was slightly higher in the group with normal ferritin compared to the group with elevated ferritin (24.4 ± 5.04% *V.S* 23.7 ± 7.8%, respectively). Fatness (function of BFP and BMI) and the ratio of total body water to lean body mass (TBW/LBM) were significantly different between the two groups of the patients (P = 0.02 and P = 0.047, respectively). However, the two groups were not significantly different in terms of the other characteristics.

In the patients with a serum ferritin level of < 1500 ng/mL, the daily intake of copper, vitamin K, vitamin B6, and fat were significantly higher compared to the patients with a ferritin level of ≥ 1500 ng/mL. Conversely, the patients with a serum ferritin level of ≥ 1500 ng/mL had a significantly higher intake of vitamin D (P = 0.045). The daily intake of energy was 1447.3 ± 261 kcal/d in the first group, while it was 1357 ± 261 kcal/d in the second group. In this regard, the difference between the groups was not significant (P = 0.12). The intake of the other nutrients was of no significant difference between the two groups (Table III).

The subsequent step was the analysis of the predictive power of fatness and TBW/LBM using binary logistic regression models. This analysis assessed their ability to classify the patients into optimum ferritin level and high ferritin level groups, as detailed in Table IV. It is notable that TBW/LBM did not demonstrate any significant predictive power in either the crude model or the adjusted model. However, in the crude model, the patients in the upper median TBW/LBM group, compared to those with TBW/LBM below the median, had a 90% higher chance of being classified in the high ferritin group (OR: 1.9, 95%CI: 0.76-4.9, P = 0.16). In the full adjustment model, this odds ratio was 3.66 (OR: 1.93.66, CI: 0.8-16.7, P = 0.16094). A significant negative correlation was observed between the fatness and serum ferritin levels in the crude model (OR: 0.19, 95%CI: 0.06-0.59, P = 0.004) and the full adjustment model (OR: 0.17, 95%CI: 0.033-0.84, P = 0.03).

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Table I: Anthropometric and biochemical characteristics of the BTM patients

Variable		Overall N = 74	Ferritin < 1500 ng/mL N = 34	Ferritin ≥ 1500 ng/mL N = 40	P-value[α]
Age (year)		21.1 ± 7.7	20.4 ± 8.4	22.6 ± 7.6	0.25
Physiologic age (year)		22.45 ± 8.4	22 ± 8.26	22.8 ± 8.5	0.94
Age of diagnosis (year)		1.1 ± 1.1	0.93 ± 0.9	1.15 ± 1.32	0.33
Blood transfusion interval (day)		22.5 ± 4.4	23.1 ± 4.3	21.7 ± 4.4	0.04
Blood transfusion volume (mL)		552 ± 252	510.7 ± 220.35	585.6 ± 272	0.39
Deferoxamine dose (vial)		4.5 ± 0.55	4.45 ± 0.63	4.5 ± 0.5	0.62
Gender	male	34 (43.3)	19 (55.9)	15 (37.5)	0.12
	female	40 (56.7)	15 (44.1)	25 (62.5)	
BMI	underweight	16 (21.6)	4 (11.8)	12 (30)	0.07
	normal	51 (68.9)	28 (82.3)	23 (57.5)	
	overweight	7 (9.5)	2 (5.9)	5 (12.5)	
	obesity	0 (0)	0 (0)	0 (0)	
Stunting (only age ≤ 18yr)	yes	10 (38.5)	6 (40)	4 (44.4)	0.83
	no	14 (61.5)	9 (60)	5 (55.6)	
Hypertension	yes	1 (1.5)	1 (2.9)	0 (0)	0.27
	no	73 (98.5)	33 (97.1)	40 (100)	
Diabetes (FBS ≥ 126mg/dl)	yes	8 (10)	4 (11.8)	4 (10)	0.81
	no	66 (90)	30 (81.2)	36 (90)	
Total cholesterol	acceptable	71 (89)	32 (94.1)	39 (97.5)	0.46
	borderline	3 (11)	2 (5.9)	1 (2.5)	
	high	0 (0)	0 (0)	0 (0)	
HDL-C	normal	15 (25.4)	10 (29.4)	5 (12.5)	0.07
	low	59 (74.6)	24 (70.6)	35 (87.5)	
Hemoglobin	acceptable(≥ 10 gr/l)	31 (38.8)	17 (50)	14 (35)	0.19
	low (< 10 gr/l)	43 (61.2)	17 (50)	26 (65)	

α: Comparison of the two groups in terms of age was done with the independent-sample T-test. Also, age of diagnosis, blood transfusion interval, and blood transfusion were compared volume with the Mann Whitney U test. The other characteristics were compared with chi-square tests.
BMI: body mass index, BTM: β-thalassemia major, HDL-C: high density lipoprotein cholesterol. FBS: fasting blood sugar

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Table II: Comparison of the body composition parameters in the BTM patients

Variable	Overall N = 74	Ferritin < 1500 ng/mL M ± SD N = 34	Ferritin ≥ 1500 ng/mL M ± SD N = 40	P-value
BFP (%)	24 ± 6.6	24.4 ± 5.04	23.7 ± 7.8	0.57#
Body fat mass (kg)	12.3 ± 5.4	12.65 ± 4.9	12.2 ± 5.8	0.52
Visceral fat (kg)	2.72 ± 4.1	2.65 ± 3.2	2.8 ± 4.8	0.23
Visceral fat area (cm^2)	48.8 ± 21.7	49.6 ± 19.54	48 ± 23.6	0.62#
Fatness (%)	-4.1 ± 11.6	-1.9 ± 7.6	-6.05 ± 14.4	**0.02**
TSF (mm)	11.1 ± 4.6	11.35 ± 4.3	10.9 ± 4.8	0.55#
LBM (kg)	36 ± 10.2	35.5 ± 11.8	36.4 ± 8.8	0.94
Soft lean mass (kg)	32.9 ± 10.2	32.2 ± 11.7	32.4 ± 8.7	0.85#
TBW (kg)	25.4 ± 7.9	24.8 ± 9.3	26 ± 6.8	0.75#
Total body protein (kg)	7.3 ± 2.2	7.3 ± 2.54	7.4 ± 1.96	0.9
Total body mineral (kg)	3.1 ± 0.75	3.3 ± 0.93	2.96 ± 0.51	0.11
TBW/LBM (%)	69.9 ± 4	68.6 ± 4.7	70.9 ± 3	**0.047**
Left upper fat mass (kg)	1.73 ± 0.54	1.7 ±0.64	1.8 ± 0.46	0.86#
Right upper fat mass (kg)	1.75 ± 0.54	1.7 ± 0.65	1.8 ± 0.44	0.85
Left lower fat mass (kg)	4.56 ± 1.4	4.5 ± 1.6	4.6 ± 1.2	0.97
Right lower fat mass (kg)	4.6 ± 1.2	4.45 ± 1.6	4.6 ± 1.2	0.8#
Trunk fat mass (kg)	13.9 ± 4.5	13.9 ± 5.4	13.8 ± 3.6	0.92#
Left upper lean mass (kg)	2.2 ± 0.7	2.15 ± 0.8	2.24 ± 0.6	0.87
Right upper lean mass (kg)	2.2 ± 0.7	2.2 ± 0.8	2.24 ± 0.6	0.88#
Left lower lean mass (kg)	5.7 ± 1.8	5.6 ± 2	5.8 ± 1.6	0.87
Right lower lean mass (kg)	5.7 ± 1.8	5.7 ± 2.1	5.8 ± 1.6	0.89
Trunk lean mass (kg)	17.7 ± 5.8	17.6 ± 7.06	17.7 ± 4.7	0.9#

M ± SD: mean ± standard deviation. The cases marked # were analyzed with the Man-Whitney test and others with the Independent T-test. BFP: body fat percentage, BTM: β-thalassemia major, LBM: lean body mass, TBW: total body water, TBW/LBM: total body water to lean body mass ratio, TSF: triceps skin fold

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Table III: Mean and standard deviation of energy intake and nutrients and their comparison with the recommended daily allowance(RDA) values in the BTM patients

Variable	Overall N = 74	Ferritin < 1500 ng/mL M ± SD N = 34	Ferritin ≥ 1500 ng/mL M ± S.D N = 40	P-value
Energy (kca/day)	1399 ± 263	1447.3 ± 261	1357 ± 261	0.12**
Protein (%from daily total energy intake)	14.7 ± 1.9	14.8 ± 1.85	14.6 ± 1.95	0.68*
Carbohydrate (% from daily total energy intake)	55 ± 4.4	54.2 ± 4.2	55.8 ± 4.4	0.11*
Fat (% from daily total energy intake)	32 ± 4.2	32.9 ± 3.7	31.3 ± 4.5	0.11**
Cholesterol (mg/dl)	135.4 ± 101	144 ± 106	128 ± 97	0.42
Fiber (gr/day)	9.2 ± 1.8	9.5 ± 1.6	9 ± 1.9	0.23**
Calcium (mg/day)	567 ± 276	583.6 ± 261	552 ± 291	0.32**
Zinc (mg/day)	6.2 ± 4.3	5.6 ±1.5	6.9 ± 5.6	0.72**
Iron (mg/day)	11.35 ± 3.7	11.2 ± 1.9	11.5 ± 4.8	0.61**
Selenium (µg/day)	13.5 ± 24	18.5 ± 28.4	9 ± 19.26	0.11**
Chromium (µg/day)	26.3 ± 0.9	26.3 ± 0.9	27.8 ± 6.7	0.95**
Magnesium (mg/day)	142 ± 27.5	148 ± 26	136.4 ± 28	0.07*
Copper (µg/day)	850 ± 21.3	900 ± 200.3	800 ± 230	**0.04***
Vit. B3 (mg/day)	13.2 ± 3	13.3 ± 3	13.3 ± 3.2	0.65**
Vit. B6 (mg/day)	1.06 ± 0.37	1.2 ± 0.3	0.95 ± 0.39	**0.004****
Folic Acid (µg/day)	287 ± 339	399.5 ± 327	297 ± 352	0.31**
Vit. B12 (µg/day)	1.96 ± 1.3	2.06 ±1.3	1.9 ± 1.2	0.47**
Ascorbic acid (mg/day)	63.4 ± 22.2	63.4 ± 18.9	63.4 ± 24.9	0.61**
Vit. D (µg/day)	3.64 ± 8.2	2 ± 5.9	5 ± 9.6	**0.045****
Vit. A (µg/day)	518.7 ± 245	543 ± 246	498 ± 247	0.29**
Vit. E (mg/day)	2.6 ± 4.7	2.65 ± 5	2.5 ± 4.5	0.79**
Vit. K (µg/day)	88.7 ± 37.1	98.6 ± 36	80 ± 36	**0.03****

M ± SD: mean ± standard deviation, * Independent samples T-test, **Man-Witney U test, BTM: β-thalassemia major

Table IV: Crude and adjustment models for the binary logistic regression of the predictive variables of serum ferritin level in the BTM patients

			OR	β	CI	P-value
Ferritin ≥ < 1500 ng/mL	TBW/LBM	Model 1	1.9	0.66	0.76 -4.9	0.16
		Model 2	2.83	1.04	0.93-8.6	0.066
		Model 3	3.66	1.3	0.8-16.7	0.094
	Fatness (%)	Model 1	0.19	-1.66	0.06-0.59	0.004
		Model 2	0.19	-1.65	0.06-0.66	0.009
		Model 3	0.17	-1.8	0.033-0.84	0.03

BTM: β-thalassemia major, OR: odds ratio, CI: confidence interval, TBW/LBM: total body water to lean body mass ratio. Model 1: Crude model, Model 2: Adjusted for age, BMI and gender, Model 3: Model 3 + additional adjustment for HDL-C level, volume of transfused blood, interval between transfusion sessions and daily intake of energy.

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Discussion

In our BTM patients, the mean daily energy intake was nearly 1400 kcal. This was not significantly different between the two groups. However, this daily energy intake was approximately 30 percent lower than the mean standard daily energy intake of 2,000 kcal. The mean daily calcium intake in both groups was 500-600 mg, which was almost half of the standard values of 1000-1200 mg. The mean daily intake of vitamin D in both groups was less than 5 µg, which was very low compared to the standard values of 10-15µg. The mean daily intake of zinc in both groups was less than 6mg, which was still lower than 10 mg, as the standard daily intake of zinc. A study on Egyptian thalassemia adolescents (28) indicated that these patients had lower intakes of energy, protein, carbohydrate, calcium and phosphorus compared to healthy children. This suggests nutritional deficiencies could impact the patients' overall health and development. Indonesian adolescents with thalassemia major also had unbalanced diets, with low protein and carbohydrate intakes but excessive fat consumption (29). Interestingly, most of them were malnourished despite adequate energy intake. In this regard, micronutrient deficiencies were notable, particularly for vitamins D and E, calcium, and folic acid. In our study, the daily intake of vitamins k and B6 and copper was significantly different in the two groups. When assessing the nutritional status, various factors should be considered, including geographical location, socioeconomic status, level of community literacy, physical activity and the nature of patients' employment. Each of these aspects can significantly affect dietary habits, ultimately impacting the overall health and well-being of patients in diverse contexts. Understanding these factors is crucial for introducing the targeted interventions that address nutritional deficiencies and improve patient outcomes. In the final analysis, we considered confounding variables such as age, gender, energy intake, medical therapy dosage, and the time interval between blood transfusion sessions.

Vitamin D plays a multifaceted role in thalassemia patients beyond the bone health. Its impact extends to enhancing immunity and cardiovascular functions, regulating the blood pressure, and even preventing cancer. The deficiencies observed in essential nutrients among thalassemia patients stems from various factors, including reduced energy intake, increased energy expenditure and protein turnover. These complexities significantly contribute to the nutritional challenges faced by BTM patients, impacting their overall health and well-being (28). Nutritional deficiencies, coupled with the consequences of iron overload due to recurrent blood transfusions, can lead to growth failure and malnutrition among BTM patients. The intake of essential nutrients in these patients frequently falls below the recommended dietary allowances (RDA) established for healthy individuals. This discrepancy arises from various factors such as physiological complications, pathological effects, inflammatory processes and diminished appetite. These factors contribute to suboptimal nutrient intake (30). Given the heightened requirement for vital nutrients in BTM patients compared to healthy individuals, a deficiency of these nutrients poses a more significant challenge (18). Indeed, a low intake of many nutrients, including calcium and vitamin D, aggravates bone problems in these patients more and more (31). Therefore, in addition to emphasizing the intake of food sources of vitamin D and calcium, supplementing of these nutrients and periodically checking the serum vitamin D levels in these patients can be effective in preventing or reducing bone abnormalities and even other disorders such as immune system disorders (32).

In both groups of our BTM patients, iron intake was lower than the standard values. Iron in food is absorbed only by 10% on average, but the iron in transfused blood, which must be injected every two or three weeks, is absorbed completely. Of course, it is still believed that iron from food sources can increase the ferritin level as much as the iron received by packed cells (33).

Reconsidering these restrictions becomes particularly crucial when we realize that limiting iron-rich food sources inadvertently restricts the intake of various other essential nutrients. Many of these nutrients share common food sources with

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iron-containing foods. Zinc, for instance, plays a critical role in various bodily functions. This realization highlights the interconnectedness of nutrients and the potential unintended consequences of restricting certain food groups. Therefore, reassessing the existing dietary recommendations for thalassemia patients, especially concerning iron and vitamin C restrictions, seems warranted to ensure adequate intake of essential nutrients (34).

The observed lower intake of zinc in our BTM patients is noteworthy. Considering the strategies to limit iron absorption, some individuals might adopt practices such as consuming excessive tea chronically with meals. However, such practices may inadvertently lead to reduced intake or absorption of other essential nutrients. For instance, the intake of milk and dairy products can be reduced with the aim of limiting the iron absorption. Calcium is essential for bone health and overall body functions, while protein is fundamental for growth and repair of tissues. Of course, it is better for these patients to increase their intake of dairy products so as to decrease the iron absorption; dairy products contain casein peptides that can inhibit iron absorption in the gastrointestinal tract with their phosphoserine clusters that bind to the iron present in the intestinal lumen, effectively inhibiting the formation of absorbable iron (35).

The low number of our participants taking supplements and mostly opting for calcium and vitamin D was a notable finding in this study. Multivitamin-mineral supplements, specifically those without added iron, can present a viable strategy and ensure adequate intake of other essential nutrients without contributing to additional iron overload.

In our study, over the 20% of the patients were underweight. Additionally, nearly 10% of them were overweight, and about 40% of those under 20 years of age were found to be short-statured. It is worth noting that, although short stature was similar in the two groups of the BTM patients, the prevalence of underweight was relatively higher in the group with elevated serum ferritin levels. Based on a similar study in the city of Yasuj (36), in the last two decades, 50% and 60% of BTM patients were underweight and stunt, respectively. This indicates the high prevalence of malnutrition in previous decades, but the growth status of patients has improved recently. This can be due to the improved provision of medical services as well as early diagnoses and screening programs before the marriage. In Malaysian (37) and Indonesian (29) cross-sectional studies, as well as several meta-analyses and systematic review studies (19, 38), the prevalence of stunting as an indicator of chronic malnutrition was higher than that in our study. In Chinese pediatric BTM patients, the prevalence of stunting was similar to that in our study (25). Several predictors such as chronic anemia, growth hormone deficiency and hypogonadism can reduce the bone growth and development in these patients. Reduced food intake due to inflammation caused by oxidant conditions in their bodies, as well as high basal energy expenditure due to increased heart work, bone marrow activity and oxygen consumption due to anemia, reduces the energy available for growth. This reduction is reflected in the lower levels of albumin and intermediate growth factor-1 (IGF-1) in BTM patients compared to healthy individuals (29). Overall, despite significant advances in medical treatments, growth deficiency is a common complication in these patients (39). These issues underscore the need for comprehensive therapeutic interventions to optimize growth potential.

In the present study, fatness and TBW/LBM in the acceptable ferritin group was higher than in the group with serum ferritin levels higher than 1500 ng/Ml. However, the fatness was lower than the optimum for both genders; the body composition analyzer device showed negative values of fatness. This low fatness and high TBW/LBM can be caused by the fact that BTM patients have low food intake due to lack of appetite, and the energy expenditure in their body is high, so their body uses fat reserves as a source of energy (21, 33, 40). The lack of association among commonly used anthropometric indices, such as BMI and serum ferritin level, may be attributed to the fact that BMI is a crude estimate of body composition and does not effectively differentiate between a fat tissue and a muscle tissue. In our study, the frequency of lipid profile disorders was not significantly different

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between the two groups, and none of the patients had hypercholesterolemia. However, it is noteworthy that, in both groups, a low HDL-C level was very common. This can be caused by anemia, blood transfusions and high blood hemolysis in these patients, which can lead to the dilution and increase of the uptake of blood lipids by macrophages (33, 41). Lipid abnormalities can also be caused by accelerated erythropoiesis leading to increased cholesterol uptake by macrophages, impaired liver function, hormonal disorders, as well as low activity of hepatic and extrahepatic lipase enzymes and rapid clearance of modified HDL and LDL by activated monocytes and macrophages (28). Given that stroke and cardiac dysfunction are the primary causes of premature death in these patients, monitoring their lipid profiles regularly seems essential.

In this study, hypertension was rare, and most the patients did not experience any high blood pressure. It is important to note that, in addition to the temporary and acute increases in the blood pressure caused by the volume of the blood transfused, which can sometimes lead to complications such as cerebral hemorrhage, thalassemia patients often experience inhibition of the sympathetic nervous system. This is due to the continuous activation of mechanical receptors in the thoracic duct resulting from ongoing blood transfusions. The experience of relatively persistent hypertension in these patients is due to vascular dilation (41-43).

Conclusion

Our study indicated a relatively high prevalence of underweight and stunting among BTM patients regardless of their serum ferritin levels. Although the corresponding growth indices are improved compared to those in the previous two decades, chronic malnutrition, notably reflected in short stature, remains a prevalent issue. Despite this improvement, the nutrient intake of the patients, both in terms of macronutrients and micronutrients, continues to fall below the standard recommendations. This underscores the persistent challenge in ensuring adequate nutrition for these patients. Furthermore, abnormalities in blood parameters such as ferritin and hemoglobin levels highlight the ongoing complexities in managing the patients' health and the importance of regular monitoring. The routine monitoring of serum vitamin D level every six months is recommended as a crucial step in addressing potential deficiencies and optimizing supplementation strategies, particularly for essential micronutrients such vitamin D and antioxidants. To enhance the comprehensiveness and applicability of future studies, it would be beneficial to include patients with minor and intermediate forms of thalassemia. This inclusion would expand the scope of the study and provide a deeper insight into the nutritional and health challenges faced across a range of thalassemia patients.

Limitations and Strengths

A key strength of this study lies in its novel approach to dietary analysis. Rather than simply comparing patients to healthy controls—a common limitation in previous research—we compared the nutrient intake of BTM patients directly against established recommended dietary standards. This provides a more meaningful benchmark for their nutritional status.Furthermore, the robustness of our findings is strengthened by two critical methodological choices: First, we used precise, invasive equipment to measure body composition, ensuring high data accuracy. Second, our statistical analysis proactively accounted for potential confounding factors—including age, gender, medication dosage, and transfusion volume—through final logistic regression models to isolate the true relationships between variables.. This cross-sectional study cannot establish causality between ferritin levels and body composition. The use of BIA and a single 24-hour dietary recall introduced measurement inaccuracy, while unaccounted confounders like chelation therapy may have influenced the results. Future longitudinal studies using more precise tools (e.g., DXA, multiple dietary recalls) while controlling for key confounders as extensive long-term studies involving larger populations and intervention protocols is recommended.

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Availability of Data

Data are available from the Corresponding author on reasonable request.

Ethical Considerations

Prior to commencing the research, the study protocol received full approval from the Ethics Committee of Yasuj University of Medical Sciences (Ethics Code: IR.YUMS.REC: 1396.25). All participants, or their parents in the case of minors, were thoroughly informed about the study's purpose and procedures. We emphasized that participation was entirely voluntary, and individuals retained the right to withdraw at any point without needing to provide a reason. To ensure transparency and trust, we guaranteed the complete confidentiality of all collected data. Written informed consent was formally obtained from each participant or their legal guardian before any study-related activities began.

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Authors' Contributions

Behrooz EbrahimzadehKour (Lead & Contact): Designed the study, led the research, analyzed the data, and wrote the first draft.Farzad Karimpour: Helped plan the study and was key in collecting and validating the data. Elaheh Piraee: Assisted with data analysis, visualization, and writing. Cirruse Salehnasab: Provided resources, supervision, and critical revision of the manuscript.

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Conflict of Interest

The authors declare no competing interests regarding this research.

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