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ORIGINAL ARTICLE

Nutritional Assessment in Patients with Transfusion Dependent β Thalassemia

Mohamed A. Mohamed[1], Abdelmoneam A. Elsayed[1], Eman M. Abdelghafar[2], Medhat M. Elamawy[1]*
[1]Internal Medicine Department, Benha Faculty of Medicine, Benha University, Qalyubia Governorate, Egypt
[2]Internal Medicine Department, Qalyoub Specialized Hospital, Ministry of Health, Qalyubia Governorate, Egypt

***Corresponding author:**
Medhat M. Elamawy

Email:
m.elamawy@fmed.bu.edu.eg

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ABSTRACT

Background: Transfusion dependent β thalassemia is a chronic inherited hemolytic anemia with defective hemoglobin β-chain. Nutritional deficiencies associations are being recognized in recent research. Although it is not fully understood, it might be related to increased nutrients needed, secondary hemochromatosis, endocrinopathies, and decreased Red Cells' life span. The aim of this study is to assess the nutritional deficiencies in Beta thalassemia major. **Methods:** A cross-sectional study on fifty transfusion dependent β thalassemia major patients ranging in age from 19 to 42 years old that were recruited from Benha Hematology Outpatient Clinic and Internal Medicine Admission wards, Benha University Hospitals, Egypt from February 2022 to November 2022. Hematological Indices like Hemoglobin, Platelets, and White Blood Cells were evaluated. Ferritin was tested in addition to Vitamin D 3 assay, Parathyroid hormone, Hb A1c, thyroid stimulating hormone, and DEXA scan. Also, extensive nutritional laboratory tests such as serum total protein, albumin, folate, calcium, Phosphorus, and Magnesium were investigated. In addition to height, weight, and routine laboratory evaluation, comprehensive history was taken. **Results**: Serum Vitamin D, folate and PTH were the most deficient in our studied patients representing 82 %, 28 %, and 20 % respectively. Also, bone mineral density was abnormal in 6 (12%) patients who had either osteopenia or osteoporosis. An increased prevalence of Type 2 Diabetes Mellitus (14%) was noted. No significant association between serum ferritin level and nutritional deficiency was found. **Conclusions**: Early assessment of nutritional deficiencies in Transfusion dependent β thalassemia is a critical step in their evaluation. Because our adult thalassaemic patient showed a lesser prevalence of the underweight category, BMI might be an inaccurate method for nutritional assessment. The vitamin D essay, serum calcium, Hb A1c, and DEXA scan should be the first screening investigations in the thalassemia patient's evaluation.

Keywords: Thalassemia; Nutritional; Body Mass Index; Ferritin

INTRODUCTION

Thalassemia is a chronic inherited hemolytic anemia with either defective hemoglobin β-chain or α-chain production and so its name, β-thalassemia, and α-thalassemia respectively. According to blood transfusion needs, thalassemia could be classified clinically as transfusion dependent and non-transfusion dependent thalassemia [1].

Thalassemia is an autosomal recessive inherited disease, so it affects both genders. Although it is more prevalent in the Mediterranean region, many health authorities assumed its presence outside the Mediterranean area [2].

In Egypt, 9.1 % of studied pediatric cord blood samples were positive PCR for α – thalassemia deletion gene. [3] Also, the prevalence of β thalassemia was studied previously by Nafei et al. who found about 1.2 % of studied children are β thalassemia carriers[4].

Clinically, thalassemic patients might have no symptoms that were incidentally discovered with the routine hematological investigation with low

Hemoglobin or only decreased Mean corpuscular volume (MCV). Also, a thalassemic patient may have marked anemia, chronic history of blood transfusions, iron overload sequels, nutritional deficiency, skeletal characteristic features, and splenomegaly [5].

Recent research recognized nutritional deficiencies and growth abnormalities in Transfusion dependent β thalassemia. Although it is not fully understood, it might be related to increased nutrient need than the daily dietary allowance, secondary hemochromatosis, endocrinopathies, and decreased life span of red blood cells (RBCs) [6].

Endocrinal manifestations include delayed growth spurts, puberty development, hypoparathyroidism, hypothyroidism, and type 2 diabetes mellitus. Multifactorial etiologies were suggested, and it might occur regardless of serum ferritin level [7]. Hypoxemia and increased metabolism could be added factors to explain most of the clinical features of thalassemic patients [8].

No single nutritional assessment domain offers complete evaluation for β thalassemia major patients. Also, the methods for classifying malnutrition are not globally accepted, so the usual rationale is to use them collectively such as Body Mass Index (BMI), height, weight, vitamin serum levels, minerals assays, bone mineralization evaluation, and Malnutrition Universal Screening Tool (MUST) score [9].

Early malnutrition screening in risky individuals such as thalassemic patients is warranted and should be detailed with the usage of multiple methods of evaluation [10].

The aim of this study is to assess nutritional deficiencies in transfusion dependent β thalassemia (Beta thalassemia major) young adult patients.

METHODS

A cross-sectional study on fifty patients with transfusion dependent β thalassemia that were recruited from Hematology Outpatient Clinic and Internal Medicine Admission wards Benha University Hospitals, Egypt from February 2022 ended in November 2022.

The study was approved by the Research Ethics Committee of Benha faculty of Medicine (M56-1-2022). Informed consent was taken from all participants upon starting the study according to the Declaration of Helsinki 2008.

Inclusion criteria were patients above 18 years old, diagnosed with chronic hemolytic anemia specifically Beta thalassemia major (blood transfusion dependent β thalassemia), and both sexes were involved.

In Beta-thalassemia major, HbF is markedly elevated up to 95 % with normal to mildly elevated HbA2. Transfusion dependent β thalassemia is a clinical term that describes severe phenotypic β thalassemic patients with regular blood transfusion for survival and attaining a normal life span. Transfusion dependent thalassemia syndrome could also encompass severe HbE/β-thalassemia, and HbH disease however our selected cases are β thalassemia group only [11].

Our selected patients are usually transfused with one packed RBC every 2-5 months.

Exclusion criteria were participants that had congenital, inherited, or systemic diseases that lead to nutritional complications other than thalassemia. Thalassemia minor and other non-thalassemia chronic hemolytic anemia were excluded. Also, patients with Hepatitis C, B, HIV, Severe cardiomyopathy, or decompensated liver diseases were excluded as it might affect the nutritional status and patient energy requirements.

Complete medical history including demographic data, chronic anemic history, frequent blood transfusion, iron chelation methods, folic acid compliance, and splenectomy was taken from every patient.

A full examination was done to evaluate the nutritional status like height, weight, Body Mass Index (BMI), signs of chronic anemia and iron overload, and unintentional weight loss.

Malnutrition Universal Screening Tool (MUST) Score was used to explore nutritional affections grade based mainly on Body Mass Index and recent weight loss. Patients were classified into one of the basic nutritional status categories as follows: 0 = low risk (well-nourished), 1 = moderate risk, and 2 = high risk for malnutrition (malnourished). Patients were at high risk if they had a BMI < 18.5, had experienced > 10% unintentional weight loss in the previous 3–6 months, or had no nutritional intake for > 5 days. They were at moderate risk if they had a BMI of 18.5–20.0 or had experienced 5–10% weight loss in the previous 3–6 months [12].

A fasting venous blood sample was taken from every patient for complete blood count (CBC), red blood cell (RBC) morphology, and differential white blood cells (WBCs). Qualitative and quantitative hemoglobin analysis, serum albumin, total protein, calcium, phosphorus, alkaline phosphatase (ALP), Hb A1c, Thyroid Stimulating Hormone (TSH), Parathyroid Hormone (PTH), and kidney function

tests were all tested. Also, blood samples were collected to assess vitamin B12 and 25-hydroxy-vitamin D (25-OH-D levels). Serum 25 (OH) D was measured by radioimmunoassay (iDS, UK). Vitamin D level of ≥30 ng/mL was defined as normal, <20 ng/mL was a deficiency, and 20-30 ng/mL was insufficient. Serum ferritin level was measured by standard methods (microparticle enzyme immunoassay). Normal ferritin value is 24 – 336 ng/ml, and 24-307 ng/ml for males and females respectively.

It was noted in many studies that serum ferritin level could predict pathological organ iron deposition if the level is between 1000 to 2500 ng/ml [13]and considered double riskier for cardiac and liver accumulation if over 2500 ng/ml, so our studied cases were categorized into 3 groups: below 1500 ng/ml, from 1500 ng/ml to 2500 ng/ml and over 2500 ng/ml[14].

Bone mineral density (BMD) was explored by doing a dual x-ray absorptiometry (DEXA) scan. Bone density is roughly denoting calcium amount per square centimeter of the studied bone. Fracture risk, osteopenia, and osteoporosis could be defined according to WHO diagnostic criteria [15]. When BMD measurement is ≥ 2.5 Standard Deviation below the reference range for a specific age, osteoporosis is diagnosed. Some limitations in using DEXA scan to determine osteoporosis in patients younger than 18 years using the T score [16].

STATISTICAL ANALYSIS

Statistical analysis was done by SPSS v26 (IBM Inc., Armonk, NY, USA). Quantitative data were evaluated for normality using Shapiro – Wilk Test and Q-Q visualizing plots. Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing ANOVA (F) test. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test. A two-tailed P value < 0.05 was considered statistically significant. Mean and standard deviation were calculated for age, height, weight, and BMI at the time of enrollment for the study. Frequency and percentages were calculated for various categories of BMI (obese, overweight, normal, underweight).

RESULTS

A total of 50 consecutive patients with transfusion dependent β-thalassemia major were included in our study. There were 27 (54%) of them males, and 23 (46 %) females. The age of patients ranged between 19 and 42 years. The mean age ± SD of study participants was 32.2 ± 8.71 years. Five (10%) patients were hypertensive, 7 (14%) patients developed diabetics, 2 (4%) patients had hyperlipidaemia, and 9 (18%) had splenectomy as shown in Table 1.

Among the studied patients, 8 (16%) patients were under weight, 35 (70%) patients were normal weight, 5 (10%) patients were overweight, and 2 (4%) patients were obese as shown in Table 1.

Hematological indices and serum ferritin were explored in Tables 2 and 3. The Hemoglobin (Hb) level of the studied patients ranged from 6 - 11.4 g/dL with a mean of 8.61 ± 1.14 g/dL. Nine (18 %) patients had mild anemia, 28 (56 %) patients had moderate anemia, and 13 (26%) patients had severe anemia.The iron overload degree of studied participants could be evaluated by serum ferritin assay as shown in table 3.

The nutritional laboratory investigations and deficiency prevalence in the studied group result were shown in Table 4. The total protein and serum albumin are normal in the studied participants. Of the studied patients, total protein ranged from 5 – 8 g/L with a mean of 7.09 ± 0.7 g/L, and albumin level is ranged from 3.5 – 5 g/L with a mean of 4.47 ± 0.37 g/L. Vitamin D, serum folate, and parathyroid hormones are the three more prevalent deficiencies.

Regarding Bone Mineral Density Study, the dual x-ray absorptiometry (DEXA) scan results showed that 44 (88%) patients had normal Bone Mineral Density while 3 (6%) patients had osteopenia, and 3 (6%) patients had osteoporosis as explored in table 5 and figure 1.

Also, the comparison between various nutritional vitamins, proteins, and minerals was studied in relation to different serum ferritin levels which reflect secondary iron overload related to chronic hemolytic anemia. No significant association was confirmed as shown in Table

Table 1: Baseline characteristic data of the studied patients

		Total (n=50)
Age (years)	**Mean ± SD**	32.2 ± 8.71
	Range	19 - 42
Sex	**Male**	27 (54%)
	Female	23 (46%)
Weight (Kg)	**Mean ± SD**	58.4 ± 8.1
Height (m)	**Mean ± SD**	1.58 ± 0.8
BMI (Kg/m^2)	**Mean ± SD**	23.6 ± 6.63
BMI category	**Underweight**	8 (16%)
	Normal weight	35 (70%)
	Overweight	5 (10%)
	Obese	2 (4%)
HB A1c %	**Mean ± SD**	6.33 ± 0.84
	Range	4 - 7.5
DM		7 (14%)
HTN		5 (10%)
Hyperlipidaemia		2 (4%)
Splenectomy		9 (18%)
MUST	**Low risk**	39 (78%)
	Medium risk	7 (14%)
	High risk	4 (8%)

BMI: body mass index, HTN: hypertension, DM: diabetes mellitus, MUST: Malnutrition Universal Screening Tool

Table 2: hematological laboratory indices in the studied population

		Total (n=50)
Hb (g/dL)	**Mean ± SD**	8.61 ± 1.14
	Mild anemia	9 (18 %)
	Moderate anemia	28 (56 %)
	Severe anemia	13 (26%)
WBCs (*10^3 cell/ µl)	**Mean ± SD**	9.64 ± 2.22
WBCs %	**Normal**	37 (74 %)
	Leucocytosis	10 (20 %)
	Leukopenia	3 (6 %)
PLT (*10^3 cell/ µl)	**Mean ± SD**	372.7 ± 98.4

Hb: Hemoglobin, WBCS: White Blood Cells, PLT: platelets

Table 3: Serum ferritin level of the studied patients

		Total (n=50)
Ferritin (ng/mL)	**Mean ± SD**	2498.5 ± 600.02
	Range	500 - 2988
	<1000 ng/mL	6 (12%)
	1000-2500 ng/mL	12 (24%)
	>2500 ng/mL	32 (64%)

Table 1: Nutritional Laboratory Tests and their Deficiency Prevalence in studied patients

	Total (n=50) Mean ± SD	Deficiency N. (%)
Total protein (g/L)	7.09 ± 0.7	0 (0%)
Albumin (g/L)	4.47 ± 0.37	0 (0%)
Vitamin B12 (pg/mL)	1.18 ± 0.55	4 (8%)
Vitamin D (ng/mL)	14.26 ± 4.68	41 (82%)
Folate (ng/mL)	5.66 ± 2.91	14 (28%)
Ca (mg/dL)	9.02 ± 0.31	7 (14%)
P (mg/dL)	4.69 ± 0.61	0 (0%)
Mg (mg/dL)	1.93 ± 0.09	2 (4%)
T4 (ng/mL)	0.88 ± 0.08	8 (16%)
PTH (pg/mL)	25.72 ± 5.55	10 (20%)

Ca: Calcium, P: Phosphorus, Mg: Magnesium, ALP: Alkaline phosphatase, TSH: Thyroid-stimulating hormone, T4: Thyroxine, PTH: Parathyroid hormone.

Table 5: DEXA results of the studied patients

	Total (n=50)
Normal	44 (88%)
Osteopenia	3 (6%)
Osteoporosis	3 (6%)

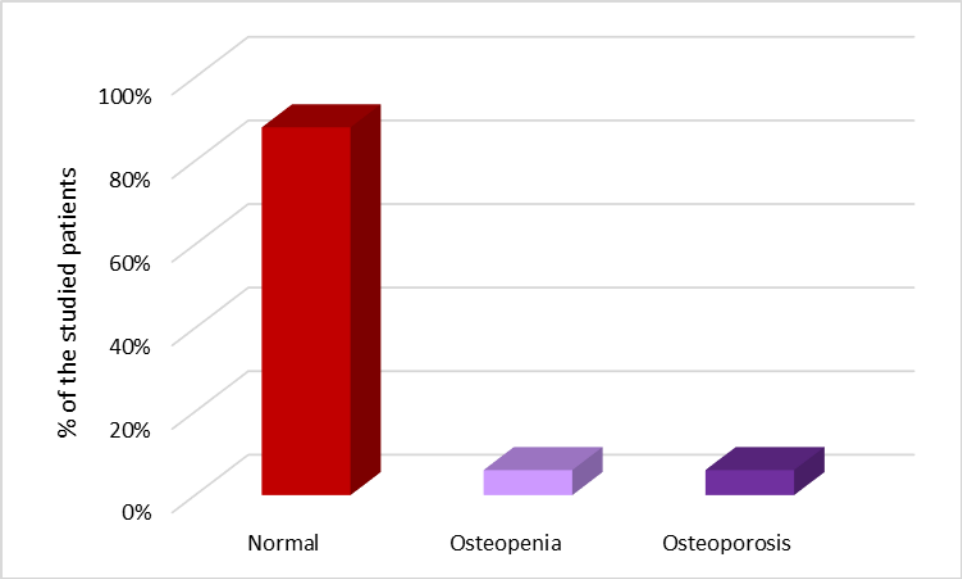
Table 6: Comparison of different variables among the ferritin-related groups

	<1000 ng/mL (n=6)	1000-2500 ng/mL (n=12)	>2500 ng/mL (n=32)	P value
Age (years)	22.33 ± 2.25	24.33 ± 2.87	22.94 ± 2.68	0.225
	19 - 26	19 - 27	19 - 27	
WBCS (10^3 cell/ µl)	9.43 ± 2.57	12.78 ± 2.14	13.23 ± 3.12	0.0601
	7 - 13	10 - 15	10 - 18	
Vitamin B12 (pg/mL)	418 ± 157.09	539.17 ± 195.46	396.41 ± 179.5	0.075
	211 - 601	160 - 749	150 - 709	
Vitamin D (ng/mL)	14.5 ± 3.67	12.17 ± 3.97	15.0 ± 4.96	0.203
	10 - 19	6 - 18	6 - 22	
Folate (ng/mL)	5.18 ± 1.39	6.2 ± 2.84	5.55 ± 3.17	0.741
	3.68 - 6.9	2.84 - 10.62	1.44 - 13.56	
Total protein (g/L)	7.12 ± 0.36	6.93 ± 0.8	7.14 ± 0.71	0.663
	6.8 - 7.7	5 - 7.9	5 - 8	

Albumin (g/L)	4.23 ± 0.54	4.58 ± 0.37	4.48 ± 0.33	0.168
	3.5 - 5	4 - 5	4 - 5	
Ca (mg/dL)	8.95 ± 0.43	8.9 ± 0.32	9.08 ± 0.26	0.179
	8.5 - 9.5	8.5 - 9.5	8.5 - 9.5	
P (mg/dL)	4.23 ± 0.82	4.59 ± 0.48	4.81±0.58	0.084
	3 - 5.2	4 - 5.2	4.1-5.8	
Mg (mg/dL)	1.9 ± 0.06	1.92 ± 0.08	1.93 ± 0.1	0.658
	1.8 - 2	1.8 - 2	1.8 - 2.1	
ALP (IU/L)	167.17 ± 32.07	164.08 ± 26.79	150.34 ± 21.01	0.117
	145 - 225	118 - 210	112 - 184	
TSH (µU/mL)	2.5 ± 0.63	2.07 ± 0.75	2.23 ± 0.45	0.299
	2 - 3.5	1 - 3	1.5 - 3	
T4 (ng/mL)	0.89 ± 0.08	0.84 ± 0.07	0.9 ± 0.08	0.065
	0.78 - 0.99	0.75 - 0.99	0.76 - 1	
PTH (pg/mL)	30.33 ± 4.8	24.58 ± 5.52	25.28 ± 5.41	0.086
	22 - 34	16 - 31	17-33	
	2-11	2 - 13	2 - 14	
HbA1c %	5.85 ± 1.3	6.63 ± 0.59	6.3 ± 0.8	0.172
	4 - 7	5.6 - 7.4	5 - 7.5	

Ca: Calcium, P: Phosphorus, Mg: Magnesium, ALP: Alkaline phosphatase, TSH: Thyroid-stimulating hormone, T4: Thyroxine, PTH: Parathyroid hormone,

Figure 1: DEXA scan results of studied participants



DISSCUSION

Thalassemia could be assumed to be a risk factor for nutritional deficiency. This can be explained by both defective erythropoiesis and decreased red blood corpuscles' life span due to inadequate bone marrow β chain production and in vivo RBCs destruction respectively [17]. These factors could explain an increase in energy and nutrient demand [18].

In our study results, much evidence of nutritional deficiency could be explored. Defective bone mineralization reflected in vitamin D deficiency (82 %), hypocalcemia (14 %), hypoparathyroidism (20 %), osteopenia (6 %), and osteoporosis (6 %) could

be one of our paramount clues on nutritional defects. This correlates to many previous studies that showed that vitamin D deficiency and insufficiency are more prevalent in thalassemic children [19].

The vitamin D essay, serum calcium, and DEXA scan should be used as screening tool in the thalassemia patient's evaluation.

Although folate deficiency is evident in our study like others, [19,20] results of serum folate in our thalassemic patients are contradictory to some local reports [21]. In a study on Egyptian thalassemic children, the authors found that folate usually tends to be higher than usual which was explained by regular folate replacement. But in our study result, serum folate tends to decrease which might be elucidated by our patients' age and loss of drug compliance with further ongoing years.

Although nutritional defects were evident in our results, only 16% of our studied patients were underweight when calculating Body Mass Index. Normal growth and puberty development are definitively affected in β thalassaemic patients [22]. One study on Iraqi thalassemic patients showed that more than half of thalassemic patients are underweight [23].

Some previous studies on adult thalassaemic patients showed a lesser prevalence of the underweight category among the studied patients. BMI might be an awkward method for nutritional assessment, especially in young adult β thalassaemic participants [20].

Recently some studies stated that BMI in β thalassemic patients may be a gender factor. They reported that the underweight category is more prevalent in male than female patients with no significant difference to matched controls [24].

The increased prevalence of Type 2 Diabetes Mellitus (14%) in our studied participants could be explained by the secondary iron overload that results from chronic hemolytic process and subsequently raised serum ferritin level. But when came to the etiologies behind other nutritional deficiencies, there are fewer reports that spot the light on these areas. It may be related to decreased nutrient intake as shown in early studies on young Italian thalassaemic patients that have a delay in their pubertal growth [25].

Although only 4 % of our studied participants were hyperlipidemia, this should be borne in mind and strictly treated because many studies recently demonstrated the risk of premature atherosclerosis in thalassemic patients even at younger ages [26].

Although a higher ferritin level would explain some nutritional clinical features of thalassemic patients such as stunted growth, endocrinopathies, and bone mineralization, [27]it could not be considered as a cause of other various deficiencies. A Turkish study recently also showed that there is no relation between higher ferritin levels and vitamin or mineral defects [19].

In thalassemic patients, nutritional deficiencies have a tremendous impact on growth development, bone mineralization, and quality of life [28].

Nutritional supplementation, especially early administration of vitamin D and zinc showed an effective impact on normal growth, musculoskeletal development, and even normal cardiac physiology that had been confirmed by many previous studies [29].

Optimum evaluation of thalassemic patients should entitle early detection of nutritional deficiencies in addition to targeting Hemoglobin level and iron overload chelating mechanisms [30].

To summarize what our study found, Vitamin D, calcium Level, and DEXA scan should be an important step in assessing the nutritional deficiency in thalassemic patients, and early insufficiency warrants interventions. Also, body weight and BMI could not definitely be used alone to assess the nutritional deficiency in thalassemic patients. Finally, many studies are needed to explore the other mechanisms that lie behind nutritional deficiency as iron overload is not the only playmaker in thalassemic nutritional defects.

Due to the limited sample size and cross-sectional study methodology, our data may not be fully generalizable to all individuals with β thalassemia.

Conflict of interest: None

Financial Disclosure: None

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