Body Composition, Dietary Intake and Biochemical Profile in Thalassemia Major Patients, Southwest of Iran

Behrooz Ebrahimzadeh Koor (✉ ebrahimzadeh1358@gmail.com)

Yasuj University of Medical Sciences

Mojtaba Yousefi

Yasuj University of Medical Sciences

Zahra Mohammadian

Yasuj University of Medical Sciences

Peyman Etemadfar

Yasuj University of Medical Sciences

Research Article

Keywords: Thalassemia, Body Composition Dietary Intake, Growth

Posted Date: December 22nd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1158458/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Thalassemia, as an autosomal recessive disorder, leads to life-threatening anemia, in which patient's life depends on long term blood transfusion and regular medical care. In this study, body composition, nutritional intake and biochemical parameters of blood transfusing dependent major thalassemia patients were evaluated.

Methods: In this cross-sectional study, 74 major thalassemia volunteers referred to educational hospital in Yasuj city were recruited. Body composition, demographic and biochemical parameters were measured. Data were statistically analyzed using parametric and non-parametric statistical tests. P-values less than 0.05 were defined as statistically significant.

Results: Data analysis showed that mean of age of participants in this cross-sectional study was 21.09 ± 7.7 years old. 21.6% of our patients were underweight, 68.9% of them were normal weight, 9.5% were overweight and none of them were obese. 8.1% of < 20 years old patients were short stature. About 80% of patients had low blood HDL concentration. About 30% of participants were at borderline levels and 42% of patients were at high and toxic levels of Ferritin. Approximately, all patients had hemoglobin lower than standard of healthy individuals. The mean body fat percent of patients was $24 \pm 6.6\%$, which was higher than the normal value ($P < 0.001$), with exception of copper, phosphorus and vitamin K and percent of protein and carbohydrates from total energy were significantly lower than standard values. The Binary logistic regression analysis also showed that the interval between sessions of blood transfusion ($P=0.03$), daily intake of vitamin D ($P=0.01$) and vitamin K ($P=0.028$) and fatness (0.006) were significant predictors of the Ferritin equation as iron overload in thalassemia patients.

Discussion and Conclusion: Malnutrition, especially underweight was evident among our patients. Intake of the energy and most nutrients were lower than standard values. Biochemical parameters such as Ferritin and hemoglobin were also abnormal. Blood levels of vitamin D in thalassemia patients should be routinely monitored. Clinical trials on the effect of supplementation with nutrients such as vitamin D and calcium and zinc are recommended. Blood levels of vitamin D in thalassemia patients should be routinely monitored every six months.

Background:

In thalassemia, the most common worldwide autosomal recessive Monogenic disease (1), lack of hemoglobin chain synthesis and ineffective the erythropoiesis (2) leads to severe anemia, in which, person life depends on continuous blood transfusions and medical care (3). According to the World Health Organization, more than 5.2% of people worldwide are thalassemia gene carrier (4) and more than 56,000 new cases of thalassemia(5) are added each year, mainly in the Middle East and Mediterranean countries (1). Bone marrow transplantation is the definitive treatment for thalassemia, but is less commonly used due to its side effects and high mortality rate (6). The common treatment procedure is the frequent blood transfusion; without it, the patients will die of severe anemia. Since each unit of blood

has about 250-300 mg of iron, which is equivalent to two years of iron absorption from the gastrointestinal tract, frequent blood transfusions in thalassemia patients cause the accumulation of iron in the body (7). Receiving an average of 25 units per year can cause the accumulation of more than 5gr irons in the body per year, which results in impaired liver, heart and endocrine gland function. Cardiac hemosiderosis with the manifestation of heart defects, arrhythmias, myocarditis, pericarditis and myocardial infarction is the cause of more than 70% of deaths in these patients(8). Iron chelation therapy is unavoidable to prevent the side effects of blood transfusion hemosiderosis. Iron Chelators prevent cells from iron toxic by removing excess of it and neutralizing free iron (9). These drugs and increased hemolysis of red blood cells, can lead to urinary excretion of the nutrients including zinc; causes anorexia, delayed puberty, reduced wound healing and short stature. Growth failure in these patients can be due to insufficient energy and essential amino acid intake and poor nutrition, followed by a decrease in insulin-like growth factor and growth hormone. Also, high oxidative stress due to lack of essential antioxidants such as vitamin C and vitamin E, as well as bone abnormalities such as osteoporosis and bone deformity from vitamin D and calcium insufficiency cause many problems for these patients(10). Food sources of iron are prohibited in these patients, while these food sources contain many other essential nutrients, so this in turn can increase the possibility of nutrient deficiency (11). Symptoms and clinical manifestations of this disease affect individual and family life. Pain, discomfort related to complications to treatment procedures, frequent absences from school and work, decreased academic performance, decreased self-esteem, feeling helpless due to dependence on others to receive care, fear of premature death and this thought that their lives are different from others, causing them isolation and depression (12,13). Various factors such as the endocrine system, nutrition and level of physical activity , In addition to age and gender, affect the body composition, all of which are impaired in thalassemia patients(14); also, overactive bone marrow, more and more accumulation of iron and impaired bone density, damage the body composition of major thalassemia patients (15,16). A study in Iran showed that 23% of thalassemia major patients were the Stunt and more than 20% of them had Hypogonadism (17). Egyptian thalassemia patients, 49% were short stature and 40% underweight (2). In the Fung EB study, patients with thalassemia, despite adequate diet, had low serum fat-soluble and water-soluble vitamins and minerals, which may indicate an increased need for some nutrients due to low absorption, high excretion or high turnover (18). A systematic review and meta-analysis study indicated that Prevalence of short stature (ST) and growth retardation (GR) were 48.9% and 41.1% respectively in Iran (18). In the other systematic review and meta-analysis study, 25% of thalassemia major patients in the worldwide had cardiac iron overload/myocardial siderosis and 42% of them had cardiac complications cardiac complications (20). In the other study, bone mineral density (BMD) and whole lean body mass (LBM) was lower in adult thalassemia patients compared with controls (21). However, the evaluation of body composition in these patients had received less attention in studies. We conducted this study to determine body composition, growth indices, nutritional intake and blood indices of thalassemia major patients in southwest of Iran.

Methods:

In this cross-sectional study, 74 patients with a definitive diagnosis of thalassemia major with at least 1 course mouthy blood transfusions were recruited by random sampling. Exclusion criteria included steroid therapy or any other drug affecting the body composition and not accompanying to end of the study (19). Participation in the study was voluntary and written consent was obtained from patients before entering the study. It should be noted that in the case of patients under 16 years old, written consent was obtained from their parents. The study protocol was reviewed and approved by the ethical committee of Yasuj University of Medical Sciences (ethics code: IR.YUMS.REC: 1396.25). Patients' weight was measured without shoes and with light clothing by a hand scale (Seca, Germany) with an accuracy of 0.1 kg. The scale was tested at the beginning and at intervals of working time with specific standard weights. Standing height of participants was also measured by a vertical scale gauge with an accuracy of 0.5 cm (Seca, Germany). Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m^2). In patients over 18 years old, BMI < 18.5 kg/m^2 were considered as underweight, 18.5-24.9 as normal weight, 25-29.9 as overweight and higher values as obesity. In participants under the age of 18y, also, according to the BMI tables, values < 3th percentile were considered as underweight, 3th-85th percentile as normal weight, 85th-95th as Overweight and values $\geq$ 95th percentile as obesity (Appendix 1, 2). Also, height values less than the 3rd percentile of the height table of the Centers for Disease Control (CDC) were considered as short stature and higher values were considered as normal height (2) (Appendix 3, 4). Blood pressure was measured using a sphygmomanometer (DDM, Inc. Casteculier, France). However, the patients must not be active before the blood pressure measurement, have not consumed heavy food, coffee, drugs and stimulant drinks and have not smoked. Dietary intake was also obtained using a 24-hour food recall questionnaire during interviews with patients. Food recall information was processed by NUT4 software. The amount of macro and micronutrients were extracted and compared with the recommended daily allowance (RDA) values. It should be noted that the energy required for each person was calculated based on three groups of 3 to 8 years old (children), 9 to 18 years old (adolescents) and $\geq$ 19 years old (adults) by standard energy formulas for the above three age groups (22). Also, the standard daily intake of protein, fat and carbohydrates were 15, 30 and 55% of total daily energy intake, respectively. Standard values for other nutrients were also determined according to standard tables (Appendix 5, 6). Body fat percent (BFP), Visceral fat mass, Subcutaneous fat mass, Visceral fat area, Body fat mass in both left and right arm, Basal metabolic rate, total energy expenditure, soft non-adipose tissue mass, Whole body water, non-adipose tissue mass, body cell mass and body mineral content were measured using a Body Composition Analyzer (ZEUS 9.9 PLUS, Korea). This device measures body composition using a non-invasive bio electrical resistance analysis method. To measure the blood parameters, after 12 hours fasting, blood sampling was done by a trained technician. Blood samples were kept at room temperature for 20 minutes and then centrifuged at 3000 rpm for 20 minutes. Their serum was then isolated and coded to reduce the likelihood of bias and human error. Total cholesterol (TC), High Density Lipoprotein cholesterol (HDL-C), ferritin and hemoglobin (Hb) were measured according to the instructions of laboratory kits (Tehran Biochemistry) by BT-3500, 3000 model of the analyser (Bio Technica Company, Italy). It should be noted that concentration of Ferritin as a long-term indicator of iron overload, up to 1500 ng/ml was considered as the acceptable upper limit values for these patients and therefore patients were divided in two groups with acceptable Ferritin level (first group)

and high Ferritin level (second group) (23) and Anthropometric and biochemical indices in these two groups were compared.

Statistical Analysis: Data were analyzed by SPSS software ((SPSS Inc., Version 26, and Chicago, IL, USA). Numerical variables were expressed as the mean $\pm$ standard (M $\pm$ S.D) and categorical ones as number (percent). The normality of the data was measured using Smirnov-Kolmogoroff test. Comparison of nutrient intake with standard values was done using Paired Samples T-test (parametric) and Wilcoxon (Nonparametric). Comparison of nutrient intake and biochemical parameters in two groups of patients based on Ferritin level was done by independent t-test and Mann-Whitney test (numerical variables) and Chi-Square test(categorical variables). The Binary Logistic regression test was used for identification of affecting variables for predicting equation of Ferritin levels. P-values less than 0.05 were considered statistically significant.

Results:

Data analysis showed that 34 patients (45.9%) had acceptable Ferritin levels and 40 patients (54.15%) had high Ferritin. The mean serum ferritin (3290 $\pm$ 360ng/ml) was much higher than normal. Even Ferritin > 18000 ng/ml there were among patients. The mean age of patients was 21.09 $\pm$ 7.7 years old. Mean systolic (96.9 $\pm$ 6.1mHg) and diastolic (60 $\pm$ 2.6mHg) blood pressure were in normal range. Serum cholesterol level (134.8 $\pm$ 26.5 mg/dl) was normal but serum HDL level (35 $\pm$ 16.3 mg/dl) was lower than normal. Hemoglobin concentration (9.6 $\pm$ 1g/l) was lower than normal, which indicates the presence of anemia.. The mean transfusion sessions intervals in two groups of patients with acceptable and high Ferritin concentration was significantly different (P=0.044), so that in the acceptable Ferritin concentration group was 23.08 $\pm$ 4.26 days, while for the group with high Ferritin was 21.69 $\pm$ 4.42 days.

According to Table 1, 21.6% of studied patients were underweight, 68.9% of them were normal weight, 9.5% were overweight and none of them were obese. The 8.1% of patients< 20 years old were Stunt. About 80% of patients had HDL concentration lower than standard values and only about 20% of them had normal HDL. More than 28% of patients were in the acceptable range of serum ferritin and about 30% of participants were in borderline values and 42% of them were in high and toxic levels. If hemoglobin (Hb) concentration >10 g/l, be considered as the goal in thalassemia patients, it can be said that about 40% of patients had acceptable Hb and in 60% of them, Hb was low. Blood pressure and cholesterol levels of almost all patients were within the normal range.

Table 1

Frequency distribution of anthropometric and biochemical parameters of thalassemia patients

variable		Number (%)	P-value ^α
Gender	Male	32(43.2)	0.043
	Female	41(56.8)	
BMI	Underweight (<18.5kg/m ²)	16(21.6)	0.162
	Normal(18.5-24.9 kg/m ²)	51(65.9)	
	Overweight (25-29.9 kg/m ²)	7(9.5)	
	Obesity (≥30 kg/m ²)	0(0)	
Stunting	yes	6(25)	0.592
	no	16(75)	
Hypertension(BP>130/85mHg)	yes	1(1.4)	0.071
	no	73(98.6)	
Diabetes(FBS≥126mg/dl)	yes	8(10.8)	0.808
	no	66(89.2)	
Cholesterol	<median(<130 mg/dl)	34(45.9)	0.522
	>median(≥130 mg/dl)	40(54.1)	
HDL	Normal(male:≥40mg/dl, Female:≥50mg/dl)	15(20.3)	0.071
	Low(male:<40mg/dl, female:<50mg/dl)	59(79.7)	
Hemoglobin	Acceptable(10 gr/l)	34(45.9)	0.143
	Low (<10 gr/l)	40(54.1)	
α : Comparison based on ferritin levels by chi-square test FBS: Fasting Blood Sugar, M: Male, F: Female.			

All patients were in normal range of cholesterol concentration; so, the comparison was done based on cholesterol median. The diabetes prevalence was about 11%. It should be noted that the frequency distribution of patients who were in different classes of these parameters were not significant difference among the two groups of patients. The gender variable was significant difference, only; 36% of patients that had high and toxic Ferritin concentration were male and 64% of them were women.

Table 2

Mean and standard deviation of body composition parameters in thalassemia patients

Variable	Mean $\pm$ Standard Deviation	P-Value (comparison of acceptable and high level of Ferritin)
Biological Age	7.8 $\pm$ 22.45	0.942 [#]
Body Fat Percent (BFP) (%)	6.6 $\pm$ 24	0.566 [#]
Body Fat Mass (kg)	5.4 $\pm$ 12.3	0.521
Visceral Fat (kg)	4.1 $\pm$ 2.72	0.235
Visceral Fat Area (cm ²)	21.7 $\pm$ 48.77	0.618 [#]
Fatness (%)	11.6 $\pm$ 4.11-	0.024
Triceps Skin Fold (mm)	4.6 $\pm$ 11.1	0.554 [#]
Lean Body Mass (LBM) (kg)	10.2 $\pm$ 35.97	0.935
Soft Lean Mass (kg)	10.15 $\pm$ 32.85	0.849 [#]
Total Body Water (TBW) (kg)	7.9 $\pm$ 25.44	0.749 [#]
Total Body Protein (kg)	2.23 $\pm$ 7.3	0.888
Total Body Mineral (kg)	0.75 $\pm$ 3.1	0.107
TBW/LBM (%)	68.86 $\pm$ 4.02	0.047
Left Upper Fat Mass (kg)	0.54 $\pm$ 1.73	0.862 [#]
Right Upper Fat Mass (kg)	1.75 $\pm$ 0.54	0.849
Left Lower Fat Mass (kg)	1.4 $\pm$ 4.56	0.974
Right Lower Fat Mass (kg)	1.4 $\pm$ 4.6	0.799 [#]
Trunk Fat Mass (kg)	4.5 $\pm$ 13.9	0.922 [#]
Left Upper Lean Mass (kg)	0.7 $\pm$ 2.2	0.866

#: Independent T-test. Others with Man-Whitney test.

Variable	Mean ± Standard Deviation	P-Value (comparison of acceptable and high level of Ferritin)
Right Upper Lean Mass (kg)	0.7±2.2	0.884 [#]
Left Lower Lean Mass (kg)	1.8±5.7	0.871
Right Lower Lean Mass (kg)	1.8±5.7	0.888
Trunk Lean Mass (kg)	5.8±17.7	0.901 [#]
[#] : Independent T-test. Others with Man-Whitney test.		

According to Table 2, the mean biological age of the patients was 22.45 ± 7.8 years, which was slightly higher than their chronological age, but not significant ($P = 0.228$). The mean BFP of patients was $24.6 \pm 6.9\%$; if we consider the standard BFP of men and women as 15% and 25%, respectively, (average of $20.54 \pm 5.5\%$), so the BFP of Participants was significantly higher than standard measures ($P < 0.001$). It should be noted that BFP in men was $20.76 \pm 6.2\%$ and in women was $26.65 \pm 5.8\%$, this means that the difference of their BFP was significant ($P < 0.001$). Also, the excess fat percent in the body of male and female patients was $6.2 \pm 5.7\%$ and $1.7 \pm 5.8\%$, respectively. However, this excess fat percent in male patients was significantly higher ($P = 0.007$). Mean SLM or body muscular tissue in patients was 32.85 ± 10.15 kg. If the standard of this measure for men and women were 45% and 36% by weight, respectively, (average of 40 ± 4.01 kg); this means that SLM of patients was less than the standard values ($P < 0.001$). The Fatness (relationship between BFP and BMI) and TBW/LBM were significantly different between two groups of patients, so that the average of these indices in the acceptable level Ferritin group was $-1.93 \pm 7.5\%$ and $68.6 \pm 4.7\%$, respectively. These values in high level Ferritin group were -6.05 ± 14 and $70.9 \pm 2.9\%$, respectively; this means that fatness was more in the first group, while the second group had more TBW/LBM.

Table 3

Mean and standard deviation of energy intake and nutrients and comparison with RDA values in thalassemia patients

Variable	Daily Intake M±S.D	Standard Daily Intake M±S.D	P-Value (Comparison with standard Values)	P-Value (comparison in two groups of Ferritin)
Daily Energy (kcal)	263.2±1398.4	450±2078.3	0.001> ^a	0.141 [*]
Protein (% from kcal)	14.7±1.9	0±15	0.459 ^b	0.501 ^{**}
Carbohydrate (%from kcal)	4.37±55.05	0±55	0.489 ^b	0.048 ^{**}
Fat (%from kcal)	4.2±32.05	0±30	0.001> ^a	0.106 [*]
Fiber (gr/day)	9.2±1.78	4.2±25.32	0.001> ^b	0.233 ^{**}
Ca (mg/day)	566.8±276.3	151.2±1044	0.001> ^b	0.324 ^{**}
Zn mg/day)	4.3±6.2	1.02±9.6	0.001> ^b	0.72 ^{**}
Fe (mg/day)	11.35±3.)	4.1±13.51	0.001 ^a	0.677 [*]
Se (µg/day)	24.1±13.5	8.8±51	0.001> ^b	0.108 ^{**}
Cru(µg/day)	26.3 ±0.9	6.7±27.8	0.001> ^b	0.951 ^{**}
P (mg/day)	161.2±659	72.5±670.8	0.802 ^a	0.173 [*]
Mg (mg/day)	27.5±141.8	89±312	0.001 ^a	0.069 [*]
Cu (µg/day)	21.3±850	12.3±850	0.893 ^b	0.043 ^{**}
Vit. B1 (mg/day)	0.23±1.08	0.23±1.4	0.001> ^b	0.464 ^{**}
Vit.B2 (mg/day)	0.27±0.84	0.23±1.4	0.001> ^a	0.124 [*]
Vit.B3 (mg/day)	3±13.2	2.2±14	0.034 ^a	0.654 [*]
Vit. B6 (mg/day)	0.37±1.06	0.28±1.89	0.001> ^a	0.003 [*]
Folic Acid (µg/day)	296.7±339.2	29.3±388	0.001> ^b	0.305 ^{**}
Vit. B12 (µg/day)	1.96±1.3	0.15±2.36	0.001> ^b	0.474 ^{**}
Ascorbic Acid (mg/day)	63.4±22.2	14.36±74.12	0.001 ^b	0.606 ^{**}

Vit.D (µg/day)	3.64±8.2	0±15	0.001> ^b	0.045 ^{**}
Vit.A (µg/day)	518.7±245	10±793.5	0.001> ^b	0.293 ^{**}
Vit.E (mg/day)	4.7±2.6	3.2±13.35	0.001> ^b	0.795 ^{**}
Vit.K (µg/day)	88.7±37.1	22.1±98.6	0.239 ^b	0.03 ^{**}
a: Paired Samples T-Test b: Wilcoxon test * Independent T-test **Man-Witney test				

According to the Table 3, total energy and intake of most nutrients, with exception of copper, phosphorus, vitamin K and the percentage of protein and carbohydrates from total energy, were significantly less than standard values. It should be noted that underweight patients consumed 50.9 ± 11.3 gr proteins; normal weight group consumed 50.3 ± 12.5 gr and overweight patients consumed 64 ± 13.4 gr ; according to the ANOWA One Way test, the third group consumed significantly more protein than the other two groups ($P = 0.021$).

Daily intake of vitamin K, D, B6 and carbohydrate percent of total energy also differed significantly based on blood ferritin levels, but intake of other nutrients did not differ significantly.

Next, due to significant differences of fatness, TBW/LBM, gender, interval between blood transfusion sessions, carbohydrate percent from total energy, daily intake of vitamin D and vitamin E in the two groups of patients (acceptable and high ferritin levels), Binary logistic regression analysis for them were implemented and the following results were obtained.

Table 4
Logistic regression analysis of influential variables in the two groups of thalassemia patients

		EX(B)	B	CI	P-Value
Ferritin (><1500ng/ml)	Session Interval(day)	0.842	0.171-	0.983-0.723	0.03
	Vit.D intake(µg/day)	1.142	0.132	1.278-1.29	0.01
	Vit.K intake(µg/day)	0.978	-0.023	0.959-0.998	0.028
	Fatness (%)	0.921	-0.171	0.723-0.984	0.006

According to Table 4, the effect of the interval between two blood transfusion sessions of blood, daily intake of vitamin D and vitamin K and fatness percent was significant in predicting the Ferritin equation (iron overload measure in thalassemia patients) and the other variables did not show a significant effect

Discussion:

In our study, the mean daily energy intake of thalassemia patients was about 1400 kcal, while the standard mean energy intake of them was more than 2000 kcal, means that they received 70% of the required standard daily energy. Although our patients had a standard 55, 15, and 30 percent contribution to the three energy-producing macro nutrient: carbohydrates, protein and fat in their diet, because the total energy was less than standard values, macronutrients intake were low. In a similar study (18) with age groups of children, adolescents and adults, the daily energy intake was estimated at an average of 1,800 kcal and the share of protein, carbohydrate, and fat was 15.7, 49.1, and 35.9 percent, respectively and daily protein intake was 71.7 ± 38 gr, While for the patients participating in our study, was 51.8 ± 12.6 gr. Calcium and vitamin D intake in our study were 566.8 ± 276.3 mg/d and 3.64 ± 8.2 , respectively, while in the same study (18), were reported 417 ± 791 mg and 3.2 ± 2.2 µg/d µg/d, respectively. In addition to its role in bone health and reducing the bone fracture risk, vitamin D can be effective in improving immunity, cardiovascular function, blood pressure and even cancer prevention. Nutritional deficiencies in thalassemia patients can be due to reduced energy intake and increased energy expenditure and increased Protein turnover (24). These nutritional deficiencies, in addition to the effects of iron overload from forced blood transfusions in these patients, can cause the growth failure and malnutrition. The nutrient intake was much lower than the RDA of healthy peoples, which can be due to physiological complications and pathological effects and the inflammatory process and loss of appetite. Although nutritional needs of thalassemia patients are higher than healthy individuals, it has been shown that their blood concentration is below the normal range. (18). Many of these nutrients play a vital role in bone health and the prevention of osteopenia. Deficiency of these nutrients can cause decreased bone mass and increased bone fracture risk (25), therefore, daily and routine supplementation of vitamin D and its periodic monitoring every six months to cover the seasonal changes were recommended for these patients(26).

In this study, iron intake was significantly lower than standard values. Apart from the fact that there is a possibility of iron deficiency in healthy people, in major thalassemia patients, the possibility of iron deficiency is more severe due to fear and anxiety from iron accumulation. Due to the fact that each unit of blood has 200 mg of iron and patients receive an average of two units of blood every three weeks, mean of 19.5 mg of iron enters the body's reserves from blood transfusion every day; Whereas, for example, the patients we studied, considering that on average 1.135 mg (11.35 mg of iron with a 10% absorption) enter their body reserves from diet (27), it does not seem that dietary iron has such an effect on iron reserves; Therefore, current common recommendations for iron and even vitamin C restriction can be reconsidered. This reconsideration becomes serious when we know that iron food sources restriction, inadvertently, results in restriction of the intake of many nutrients such as zinc, because their food sources, mostly, are same. Zinc is necessary for maintaining the immune system, bone health, growth, cell division and differentiation, gene expression and thyroid hormone function, metabolism of vitamin A and testosterone (28, 29).

In our study, zinc intake was lower than standard values. When, strategies such as excessive and chronic consumption of tea with food is taken into consideration to reducing iron absorption, it can reduce milk and dairy intake, which are rich sources of nutrients such as zinc, calcium and protein needed for growth.

In our study, only about 30% of people reported taking supplements, most of which were calcium and vitamin D. However, multivitamin-mineral supplements with no iron, due to their role in providing daily need of many vitamins and minerals can be a suitable strategy.

More than 21% of our patients were underweight, 69% had normal weight, a little over 9% were overweight and none were obese. 25% of patients <20 years old were short stature. A study conducted about 20 years ago on thalassemia major patients referred to the our studied hospital(30) found that more than 65% of thalassemia patients were Stunt and more than 50% were underweight. A comparison of the results of these two studies suggests the improvement of growth indices in patients with thalassemia major in Yasuj city (Kohkiluyeh and Boyerahmad Province), which can be from health services improvment and increase the patients' awareness. In a European study, 18% of thalassemia adolescents had stunted growth (31), which was consistent with the results of our study. A meta-analysis study on the growth indices of Iranian thalassemia patients (32) showed that the rate of short stature in Iranian thalassemia patients is very high and more than 50% of patients have short stature. In the latest review and meta-analysis of studies conducted worldwide (33), the short stature of thalassemia major patients was estimated at 48.9%.

FBP was significantly higher than the standard values in our patients; the excess fat percent (more than the standard values for any gender) was higher in male patients than females. LBM of the patients was less than the standard. The fatness was higher in the group with acceptable Ferritin than in high level Ferritin group, while the TBW/LBM was exactly opposite. In most other studies, the body composition of thalassemia major patients was compared with healthy individuals and even with thalassemia minor patients and the differences in body composition of major thalassemia and minor patients were shown (21,34). Some studies have shown a decrease in fat mass and an increase in the muscle mass of these patients (24). Different and sometimes contradictory results of different studies on fat mass and muscle tissue in thalassemia patients can be attributed to the rate of progression and the prevalence of malnutrition in these patients because the more the malnutrition indicates that these patients use more their body fat reserves. Therefore, the adipose tissue in their body decreases and therefore the percentage of muscle tissue increases. Also, if the prevalence of malnutrition is low, the better control of this disease and patients' bodies has not used fat reserves. It should be noted that the analysis of body composition can be examined using various components. In two-component analysis, fat mass (FM) and LBM are examined. LBM includes soft lean mass (SLM) and whole body mineral; Therefore, three-component analysis includes FM, SLM and whole body mineral. Since SLM contains total body water (TBW) and total body protein (TBP), it can be said that the four-component analysis includes FM, whole body mineral, TBW and TBP.

In our study, mean blood cholesterol concentration was low, which was apparently desirable, but blood HDL was also lower than normal. It should be noted that lipid profile abnormality has been identified in a few studies, but almost all of them indicated a decrease of lipid profiles in these patients (24). Lipid profile abnormality can be due to blood dilution from anemia, increased cholesterol macrophage uptake due to accelerated Erythropoiesis, decreased hepatic and non-hepatic Lipase enzyme activity, rapid uptake of altered LDL and HDL by the Monocytes and macrophages and iron accumulation (35). Because these biomarkers are used to assess the cardiovascular function, regular monitoring of lipid profiles in these high-risk patients was recommended.

In our study, serum ferritin level was high and hemoglobin was low, which can lead to an increase the iron absorption from the diet, which exacerbates the problem of iron accumulation. In our study, 42% of patients had Ferritin concentration > 2000 ng/ml; even in some studies (36), more than 60% of thalassemia patients had Ferritin > 2000 ng/ml. After transfusing 20 units of dense red blood cells, the amount of excess iron reaches 4gr, which is equivalent to the iron stores of an adult male. This accumulation of iron is inevitable because there is no way to excrete it from the body. Accumulation of excess iron in the body can cause complications such as enlarged liver, spleen, cardiomyopathy, growth and development abnormality, hypothyroidism, diabetes and premature death. Pathologically, tissue damage is attributed to active radicals such as hydroxyl free radicals that can cause the damage of proteins, fats and even DNA. Therefore, evaluation of an indicator of excess iron load on a regular basis is necessary, which in most cases, blood Ferritin is considered as an indicator of iron accumulation in the body (37, 38); but it is an indirect method of estimating iron accumulation and Some genetic arrangements of specific genes such as HFE gene (human factors engineering), Transferrin gene and other genes involved in iron accumulation and therefore the interpretation of blood Ferritin level is complex (36).

Our patients had normal blood pressure or predisposed to hypotension, which other studies have also come to this conclusion to some extent (39); this despite the continuous blood transfusion can; because the increase in blood volume due to long-term blood transfusion causes the stimulation of mechanical receptors in the thoracic duct, which in turn leads to inhibition of sympathetic nerve activity and this causes long-term hypotension in thalassemia patients. However, immediately after blood transfusion, due to a sudden increase in blood volume, the blood pressure increases, which can lead to confusion or even cerebral hemorrhage (40-42).

From the strengths of the study, in addition to analyzing the body composition using a standard device, is the comparison of nutritional intake of patients with the recommended standard values, while in most previous studies was compared with that of healthy individuals.

Limitation of our study were its cross-sectional design and relatively low number of patients, while to discover the causal relationships requires long-term studies with a larger population and even intervention studies.

Conclusion:

In our patients, decrease of growth indices was quite evident and malnutrition, especially chronic malnutrition, was observed as short stature. Although growth indices of our blood transfusion dependent major thalassemia patients showed a marked improvement compared to the previous decade, their intake of nutrients, both macronutrients and micronutrients, was still lower than the standard recommended amounts. Blood parameters such as ferritin and hemoglobin were also abnormal. Routine monitoring of vitamin D in thalassemia patients every six months and interventional clinical trial studies of supplementation with many micronutrients such as vitamin D and antioxidants are recommended. In future studies, it is recommended to include minor and the Intermedia patients in the Subsequent studies to generalization of the study results.

Abbreviations:

ST: short stature; GF: growth retardation; BMD: bone mineral density; FM: Fat mass; Hb: Hemoglobin; HFE: human factors engineering; LBM: lean body mass; BMI: body mass index; CDC: centers for disease control; RDA: recommended daily allowance; BFP:body fat percent; FM: fat mass ; LBM:lean body mass; TBW: total body water; TBP: total body protein; SLM:soft lean mass; LDL:low density lipoprotein; HDL:high density lipoprotein; DNA: Deoxyribonucleic acid.

Declarations:

Ethics approval and consent to participate Ethics:

This cross-sectional study was conducted in accordance with the ethical guidelines of the Helsinki Declaration of and was reviewed and approved by the ethical committee of Yasuj University of Medical Sciences (ethics code: IR.YUMS.REC: 1396.25). Prior to the study, written consent was obtained from patients or their parents (patients<16yr) and a commitment was made that patient information would remain confidential.

Consent for publication:

Not applicable.

Availability of data and materials:

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request for data requests.

Competing interests:

All authors declare that they have no competing interests.

Funding:

This study was supported by Vice Chancellor for Research, Yasouj University of Medical Sciences. (ethics code: IR.YUMS.REC: 1396.25).

Authors' contributions:

BEK designed and supervised the study wrote the preliminary manuscript. MY and Zm were actively involved in the field work and entering data in analytical software. PE involved in finalizing of manuscript and scientific editing. All statistical analysis done by BEK.

Acknowledgements:

The authors thank the thalassemia patients of Yasuj city for participation in this study and Laboratory unit and Thalassemia Unit staff of Shahid Beheshti Hospital for their sincere cooperation.

References:

1. Weatherall DJ. Hemoglobinopathies worldwide: present and future. *Curr Mol Med*. 2008;8(7):592-599. doi:10.2174/156652408786241375
2. Fahim FM, Saad K, Askar EA, Eldin EN, Thabet AF. Growth Parameters and Vitamin D status in Children with Thalassemia Major in Upper Egypt. *Int J Hematol Oncol Stem Cell Res*. 2013;7(4):10-14
3. Canatan D, Ratip S, Kaptan S, Cosan R. Psychosocial burden of beta-thalassaemia major in Antalya, south Turkey. *Soc Sci Med*. 2003;56(4):815-819. doi:10.1016/s0277-9536(02)00080-1
4. World Health Organization (WHO). Global epidemiology of hemoglobin disorders and derived service indicators. Available from: <https://www.who.int/bulletin/volumes/86/6/06-036673/en/>. Accessed 11 January 2020.
5. Abu-Shaheen A, Heena H, Nofal A, et al. Epidemiology of Thalassemia in Gulf Cooperation Council Countries: A Systematic Review. *Biomed Res Int*. 2020;2020:1509501. Published 2020 Oct 28. doi:10.1155/2020/1509501
6. Rund D, Rachmilewitz E. β -Thalassemia. *N Engl J Med* 2005; 353:1135-46.
7. Fauci, Bethesda, j. Larry Jameson, Hemoglobinopathy In: Braunwarld. Kasper. Hauser . Longo . Jameson . Loscalzo . *Harrisons Internal Medicine*
8. Borgna-Pignatti C, Rugolotto S, De Stefano P, Piga A, Di Gregorio F, Gamberini MR, et al. Survival and disease complications in thalassemia major. *Ann N Y Acad Sci*. 1998 Jun; 850:227-31.
9. Prabhu R, Prabhu V, Prabhu RS. Iron overload in beta thalassemia – A review. *J Biosci Tech*. 2009; 1(1): 20-31
10. Tiosano D, Hochberg Z. Endocrine complications of thalassemia. *J Endocrinol Invest*. 2001;24(9):716-723. doi:10.1007/BF03343916

11. Soliman AT, El-Matary W, Fattah MM, Nasr IS, El Alaily RK, Thabet MA. The effect of high-calorie diet on nutritional parameters of children with beta-thalassaemia major. *Clin Nutr.* 2004; 23: 1153-8
12. Telfer P, Constantinidou G, Andreou P, Christou S, Modell B, Angastiniotis M. Quality of life in thalassemia. *Ann N Y Acad Sci.* 2005; 1054: 273-82.
13. Mikelli A, Tsiantis J. Depressive syndromes and quality of life in adolescents with thalassemia. *J Adolescence.* 2004; 27(2): 213-6
14. Rosen C. J., Klibanski A. Bone, fat, and body composition: evolving concepts in the pathogenesis of osteoporosis. *The American Journal of Medicine.* 2009; **122**(5):409–414
15. De Sanctis V., Soliman A. T., Elsedfy H., et al. Growth and endocrine disorders in thalassemia: the international network on endocrine complications in thalassemia (I-CET) position statement and guidelines. *Indian Journal of Endocrinology and Metabolism.* 2013; **17**(1):8–18
16. Casale M., Citarella S., Filosa A., et al. Endocrine function and bone disease during long-term chelation therapy with deferasirox in patients with β -thalassemia major. *American Journal of Hematology.* 2014; **89**(12):1102–1106
17. Shamshirsaz A, Bekheirnia MR, Kamgar M, et al. Metabolic and endocrinologic complications in betathalassemia major: amulticenter study in Tehran. *BMC Endocr Disord.* 2003; 12: 3-4
18. Fung EB. Nutritional deficiencies in patients with thalassemia. *Ann N Y Acad Sci.* 2010 Aug;1202:188-96
19. Arab-Zozani M, Kheyrandish S, Rastgar A, Miri-Moghaddam E. A Systematic Review and Meta-Analysis of Stature Growth Complications in β -thalassemia Major Patients. *Ann Glob Health.* 2021; **87**(1):48
20. Koohi, F., Kazemi, T. & Miri-Moghaddam, E. Cardiac complications and iron overload in beta thalassemia major patients—a systematic review and meta-analysis. *Ann Hematol.* 2019; **98**:1323–1331.
21. Vlychou M, Alexiou E, Thriskos P, Fezoulidis I, Vassiou K. Body Composition in Adult Patients with Thalassemia Major. *Int J Endocrinol.* 2016; 2016:6218437. doi:10.1155/2016/6218437
22. L.Kathleen Mahan & Janice L Raymond. Krause and Mahan's Food & The Nutrition Care Process 14th edition(2020). Chapter2. PP:23
23. Hadaegh F, Zare S, Tohidi M. Growth and puberty disorders in major thalassaemic patients in Hormozgan. *Iranian Journal of Endocrinology and Metabolism.* 2003; 5 (3) :187-193[in persian].
24. Elalfy MS, Ebeid FSE, El Gendy YG, Zaki MM, Kalifa ASA. Body Composition in Egyptian Children With Transfusion-dependent Thalassemia: The Impact of Nutrition and Metabolic Profile. *J Pediatr Hematol Oncol.* 2020 Jul;42(5):e334-e339. doi: 10.1097/MPH.0000000000001712. PMID: 31929387
25. Ellen B. Fung, Yan Xu, Felicia Trachtenberg and et all. Inadequate Dietary Intake in Patients with Thalassemia. *J Acad Nutr Diet.* 2012 July ; 112(7): 980–990. doi:10.1016/j.jand.2012.01.017
26. Fung EB, Aguilar C, Micaily I, Foote D, Lal A. Treatment of vitamin D deficiency in transfusiondependent thalassemia. *Am J Hematol.* 2011; 86(10):871–873. [PubMed: 21818763]

27. De Alarcon PA, Donovan ME, Forbes GB, Landaw SA, Stockman JA. Iron absorption in the thalassemia syndromes and its inhibition by tea. *N Engl J Med*. 1979; 300(1):5–8. [PubMed: 758174]
28. Shamshirsaz AA, Bekheirnia MR, Kamgar M, et al. Bone mineral density in Iranian adolescents and young adults with beta-thalassemia major. *Pediatr Hematol Oncol*. 2007; 24(7):469–479. [PubMed: 17786783]
29. Fikry SI, Saleh SA, Sarkis NN, Mangoud H. Study of serum zinc in relation to nutritional status among thalassemia patients in Damanhour Medical National Institute. *J Egypt Public Health Assoc*. 2003; 78(1–2):73–93. [PubMed: 17219912]
30. Nabavizadeh S, Haghbin S, Khosravi A. Evaluation of the Growth Parameters in Major Thalassemic Patients . *Armaghane danesh*. 2005; 10 (2) :53-58[in persian].
31. Caruso-Nicoletti M, De Sanctis V, Capra M, Cardinale G, Cuccia L, Di Gregorio F, Filosa A, Galati MC, Lauriola A, Malizia R, Mangiagli A, Massolo F, Mastrangelo C, Meo A, Messina MF, Ponzi G, Raiola G, Ruggiero L, Tamborino G, Saviano A. Short stature and body proportion in thalassaemia. *J Pediatr Endocrinol Metab*. 1998;11 Suppl 3:811-6. PMID: 10091151
32. Badfar, Gholamreza, et al. "Prevalence of short stature, underweight and delayed puberty in Iranian patients with thalassemia major: a systematic review and meta-analysis." *Iranian Journal of Pediatric Hematology and Oncology* 7.4 (2017): 245-259
33. Arab-Zozani M, Kheyrandish S, Rastgar A, Miri-Moghaddam E. A Systematic Review and Meta-Analysis of Stature Growth Complications in β -thalassemia Major Patients. *Ann Glob Health*. 2021 Jun 8;87(1):48. doi: 10.5334/aogh.3184. PMID: 34164261; PMCID: PMC8194969
34. Fung E. B., Xu Y., Kwiatkowski J. L., et al. Relationship between chronic transfusion therapy and body composition in subjects with thalassemia. *Journal of Pediatrics*. 2010;**157**(4):641–647
35. Papanastasiou DA, Siorokou T, Haliotis FA. Beta-thalassaemia and factors affecting the metabolism of lipids and lipoproteins. *Haematologia (Budap)*. 1996;27:143–153.
36. Atmakusuma TD, Lubis AM. Correlation of Serum Ferritin and Liver Iron Concentration with Transient Liver Elastography in Adult Thalassemia Intermedia Patients with Blood Transfusion. *J Blood Med*. 2021 Apr 15;12:235-243. doi: 10.2147/JBM.S303703. PMID: 33883962; PMCID: PMC8055280.
37. [6th international TIF educational work shop on clinical management of thalassemia.NOV 1999.pp\(60-63\)](#)
38. Nathan.G.D, Oskin.S.H : Hematology of infancy and children 5thed.1998.published by W.B.Sanders Co.pp(855-59)
39. Veglio F, Melchio R, Rabbia F, Molino P, Genova GC, Martini G, Schiavone D, Piga A, Chiandussi L. Blood pressure and heart rate in young thalassemia major patients. *Am J Hypertens*. 1998 May;11(5):539-47. doi: 10.1016/s0895-7061(97)00263-x. PMID: 9633789
40. Wasi P, Pootrakul P, Piankijagum A, et al: A syndrome of hypertension, convulsion and cerebral haemorrhage in thalassemic patients after multiple blood-transfusion. *Lancet* 1978;ii:602–604.
41. Royal JE, Seeler RA: Hypertension, convulsions, and cerebral haemorrhage in sickle-cell anaemia patients after blood transfusions (letter). *Lancet* 1978;ii:1207

42. Tanphaichitr VS, Suvatte V, Mahasandana C, Tuchinda S: Hypertension posttransfusion in Thai thalassemic children: early detection and management (original article series). Birth Defects 1988;23(5B):251–255

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Appendix12.doc](#)
- [Appendix34.doc](#)
- [Appendix56.doc](#)