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ORIGINAL ARTICLE

Factors affecting nutritional status among pediatric patients with transfusion-dependent beta thalassemia

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Abstract Malnutrition affects the growth, efficacy of treatments and quality of life in children suffering from thalassemia. This study was conducted to assess the nutritional status of thalassemic patients and to determine the factors involved. Data were obtained from 140 thalassemic patients aged 8–18 years in Mashhad, Iran, on anthropometry, food record and biochemical profile. The prevalence of malnutrition was 44.3 % for boys and 19.6 % for girls, as determined by low body mass index. Furthermore, 44.3 % of boys and 37.7 % of girls were found to be of short stature. Sum of triceps and subscapular skinfold thickness and arm muscle area (AMA) calculation showed the incidence of 7.4 % leanness and 60.7 % wasting among thalassemic children and adolescents. The average of energy intake met 74 % of recommended dietary allowance, although more than 71 % under-reporting was calculated for food records. The intake of energy, macronutrients, zinc, iron and vitamin E was positively correlated ($P < 0.05$) with anthropometric measures. Age, age at first transfusion, age of starting chelation and serum alkaline phosphatase were considered as positive predictors for nutritional status, whereas puberty, gender and fasting blood sugar as negative predictors. Nutritional status of thalassemic children and adolescents should be monitored, focusing on their nutrition education and supplementation, treatment protocol and control on blood sugar. These may play important roles in enhancing the quality of life in thalassemic children and adolescents.

Keywords Malnutrition · Short stature · Diet · Children · Thalassemia

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Introduction

Beta thalassemia syndromes are the most common hereditary hemoglobinopathies. The incidence may be as high as 10 % in Asian countries [1]. Growth failure in thalassemic children has been attributed to growth hormone deficiency, hypothyroidism, delayed sexual maturation, hypogonadism, diabetes mellitus, zinc deficit, low hemoglobin levels, bone disorders and desferrioxamine toxicity [2]. Transfused thalassemic children develop iron overload complications, which include growth retardation and failure or delay in sexual maturation [3].

The incidence of 18 % for short stature and another 40 % for short upper trunk among 476 Italian 2–36 years

old thalassemic patients, 65.7 % short stature among 146 Iranian 10–22 years old thalassemic patients, 24 % underweight accompanying 33 % short stature in 154 Indian thalassemic children and adolescents, and high prevalence of impaired growth velocity among 26 Malaysian pre-pubertal thalassemic patients (57.7 %) compared to healthy control group (19.2 %) showed that malnutrition and growth impairment is commonly seen in children with thalassemia despite regular blood transfusions and desferrioxamine treatments [4–7]. Growth failure in thalassemic children may be attributed to growth hormone deficiency, hypothyroidism, delayed sexual maturation, hypogonadism, diabetes mellitus, zinc deficit, low hemoglobin levels, bone disorders and desferrioxamine toxicity [2].

Growth retardation in beta thalassemic children, which was demonstrated by low body mass index (BMI) and short stature, was approved in different countries [2, 5, 6, 8, 9]. They may develop some degree of malnutrition. Hence, the main aim of the present study was to determine the factors influencing the nutritional status of thalassemic children.

Materials and methods

This cross-sectional study was conducted in the specialized center for Thalassemia in Mashhad, Iran. Prior ethical approval was obtained from Mashhad University of Medical Science, Research Council. Using convenient sampling, a sample of 140 transfusion-dependent beta thalassemic children and adolescents aged between 8 and 18 years were selected to participate in this study. Informed consent was obtained from their parents. Using convenient sampling, thalassemic patients with mal-absorption diseases, other gastrointestinal problems and asthma, patients currently taking a bisphosphonate medication for osteopenia, patients who have had a bone marrow transplant and the individuals with chronic use of systemic corticosteroids were excluded from this study. The socioeconomic information, disease history, blood transfusion and chelation therapy details were assessed using a questionnaire administered during the interview with parents. The children's food consumption was evaluated by the combination of the 24-h diet recall and 2-day food record. Dietary intake was evaluated as the percent of recommended dietary allowance (RDA) for age and gender for specific nutrients and energy [10].

Anthropometric measurements [height, weight, triceps and subscapular skinfold thickness, mid upper arm circumference (MUAC) and waist circumference (WC)] of subjects were taken. The measurements were taken according to international guidelines [11] by the same person for all subjects. Frisancho (1990) [12] category for the sum of triceps and subscapular skinfold thickness was applied to determine the nutritional status of subjects based on their skinfold thickness. Body mass index (BMI), arm muscle area (AMA), Z-scores for height-for-age, weight-for-age and body mass index for age were calculated and used to determine the nutritional status of subjects [10, 12]. Pre-transfusion serum hemoglobin, fasting blood sugar (FBS), serum ferritin and thyroid function test (TSH, T_4) were obtained from the patient's file based on the more recent test results.

Statistical analyses

The data were analyzed using Statistical Package for the Social Sciences (SPSS), version 16. All values were reported as the mean and standard deviation. Pearson correlations coefficients were used to determine relationships anthropometric parameters and the intake of energy and nutrients. For data which were not in normal distribution, Spearman's correlation was performed to show the relationship between variables. Multiple Regression was conducted to determine the predictors of nutritional status in the study subjects by specifying the confounding factors in this study. Prevalence rate was expressed with 95 % confidence intervals. In this study, the statistical significance and power were considered at a P value <0.05 and 80 %, respectively.

Results

Assessing the economic status of family showed that more than 65 % of subjects were accounted by low income families. Study population included 56.4 % boys and 43.6 % girls. Based on the appearance of secondary sexual characteristics, which were reported by parents, 22 % of subjects were in post-pubertal stage. Mean values for age, age at the initiation of blood transfusion and chelation therapy, anthropometric parameters and biochemical profile by gender were shown in Table 1. Desferal was the most common iron chelator which was used regularly, 3–6 times/week, by more than 64 % of subjects. According to Height-for-Age Z score category, 58.6 % of subjects suffered from some degree of malnutrition (mild, moderate, severe) which was more common among girls (60.7 %) when compared to boys (57 %). Applying Weight-for-Age, Z score malnutrition was seen in 73 % of subjects. Malnutrition was present in 82 % of boys and 70.6 % of girls. Short stature, defined as—2SD of mean height was present in 41.4 % of thalassemic subjects in this study as was shown in Fig 1. In the evaluation of age-adjusted body mass index (BMI), using WHO BMI Z score charts (2007), 33.6 % of subjects were determined to be underweight which was more common in boys as shown in Fig 2. According to sum of triceps and subscapular skinfold

Table 1 Distribution of age, anthropometric characteristics and bone density indices of subjects (Presented as Mean ± SD)

Characteristic	Boys ($n = 79$)		Girls ($n = 61$)		Total ($n = 140$)
	8–12 years ($n = 29$)	13–18 years ($n = 50$)	8–12 years ($n = 30$)	13–18 years ($n = 31$)	Mean ± SD (Range)
Age (year)	10.00 ± 1.5	16.54 ± 1.8#	9.4 ± 1.5	16 ± 2#	13.5 ± 3.7 (8–18)
Age of diagnosis (months)	9.1 ± 8.2	17.8 ± 22.8	11 ± 12.4	21.6 ± 33.7	15.4 ± 22.3 (1–120)
Age of first transfusion (months)	12.1 ± 18.1	20.3 ± 24.8	14.6 ± 14	22.1 ± 33.6	17.8 ± 24.1 (1–120)
Age of start of chelation (months)	38 ± 24.4	47.1 ± 40	45.3 ± 31	53.5 ± 38.4	46.1 ± 34.8 (0–168)
Height (cm)	131.3 ± 9.4	156.9 ± 11.8*	126.2 ± 9.4	150.2 ± 9*	143.5 ± 16.5 (106.2–178)
Weight (kg)	27.8 ± 5.9	44.9 ± 10.7*	24.8 ± 5	43.8 ± 9.1*	36.8 ± 12.3 (15–66)
Weight/Height (%)	21 ± 3.3	28.3 ± 5.2*	19.4 ± 2.7	28.9 ± 4.7*	25 ± 5.9 (14.1–40.8)
BMI (kg/m^2)	16.2 ± 1.9	18.4 ± 2.7*	15.6 ± 1.6	19.6 ± 2.8*	17.6 ± 2.8 (13.3–26.4)
WC (cm)	61.4 ± 5.8	71.4 ± 7.4*	58.6 ± 4.8	70.8 ± 6*	66.5 ± 8.4 (49.7–87)
Triceps skinfold (mm)	9.6 ± 3.7	10.8 ± 4	10.8 ± 2.8	16.3 ± 5*	11.7 ± 4.6 (4.6–26.7)
Subscapular skinfold (mm)	6.2 ± 3.5	7.8 ± 3#	6.4 ± 2.5	13.3 ± 5.7#	8.3 ± 4.6 (3.4–23.2)
MUAC (cm)	18.1 ± 2.4	21.8 ± 2.8*	17.8 ± 1.8	23.1 ± 3*	20.5 ± 3.4 (14–30.5)
Arm muscle area (AMA)	15.1 ± 1.5	18.4 ± 2.4*	14.5 ± 1.4	18 ± 1.9*	16.8 ± 2.6 (11.6–25.6)
Pre-transfusion Hb (g/dl)#	9.4 ± 0.4	9.5 ± 0.8	9.5 ± 0.6	9.8 ± 0.6	9.5 ± 0.7 (7.8–11.4)
Serum ferritin (ng/ml)	5,284 ± 6,386	5,232 ± 4,383	4,415 ± 4,118	5,204 ± 4,565	5,052.3 ± 4,831.5 (200–26,850)
Serum TSH (μU/ml)	2.5 ± 1.4	2.4 ± 1.1	2.7 ± 1.8	2.4 ± 1.6	2.5 ± 1.4 (0.1–9.8)
T_4 (μg/dl)	8.5 ± 1.6	7.8 ± 1.7	8.3 ± 2	8.7 ± 2.2	8.2 ± 1.9 (2.8–13)
FBS (mg/dl)	89.8 ± 9.2	113.8 ± 69#	99.6 ± 55	108.2 ± 53	104.2 ± 54.8 (58–435)

Significant level $P < 0.05$

TSH thyroid stimulating hormone, *T4* thyroid hormone, *FBS* fasting blood sugar

* Independent Sample *T* test

\# Mann–Whitney test (comparison between groups)

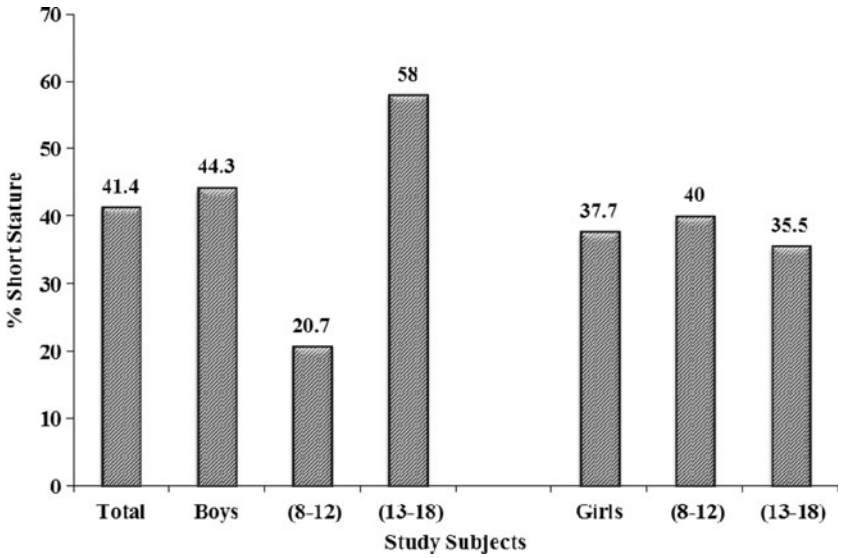

Fig. 1 Percentage of short stature, according to age and gender, in study subjects

thickness, 7.4 % of subjects were categorized as lean and 18.5 % were below the average for sum of triceps and subscapular skinfold. Based on AMA categorization, 60.7 % of subjects were in wasting category. The details were summarized in Table 2.

Given the high percentage of under-reporting in food intake record in this study (71 %), only normal-reported data ($n = 40$) in analyses provided more accurate results. Evaluation of nutrient intake showed that the intake of energy was 74 % of the recommendation (RDA) which

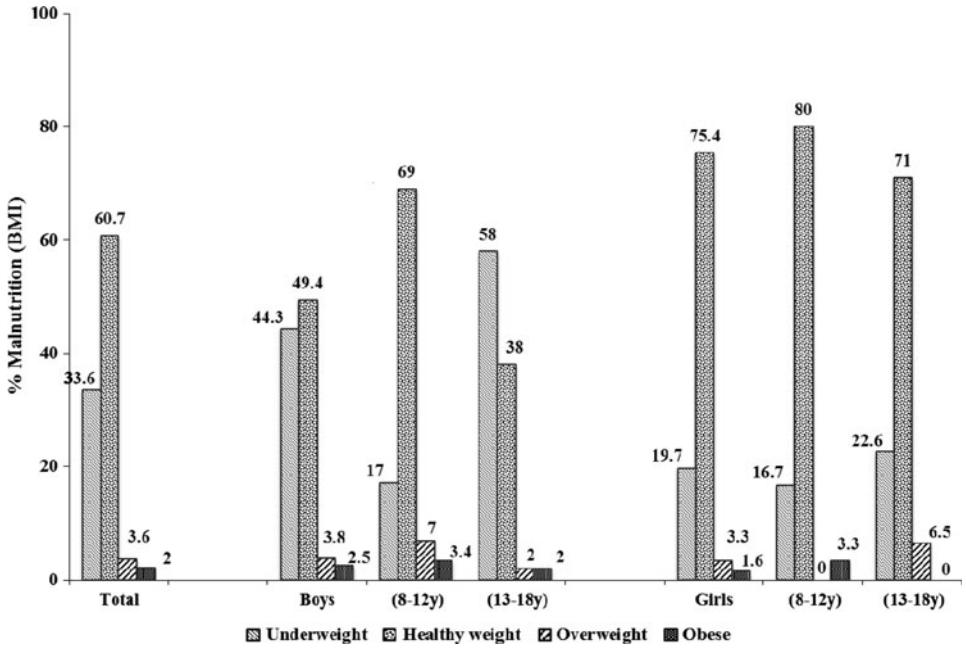

Fig. 2 Percentage of malnutrition based on BMI Z score of study subjects

Table 2 Nutritional status of subjects according to sum of triceps and subscapular skinfolds and arm muscle area [Presented as *n* (%)]

Nutritional assessment	Total	Boys		Girls	
	(8–18 years)	(8–12 years)	(13–18 years)	(8–12 years)	(13–18 years)
Sum triceps and subscapular skinfold categories					
Lean	8 (7.4)	0 (0.0)	5 (12.5)	1 (4.3)	2 (8.7)
Below average	20 (18.5)	4 (18.2)	7 (17.5)	7 (30.4)	2 (8.7)
Average	72 (66.7)	17 (77.3)	25 (62.5)	12 (52.2)	18 (78.3)
Above average	4 (3.6)	0 (0.0)	3 (7.5)	1 (4.3)	0 (0.0)
Excess fat	4 (3.7)	1 (4.5)	0 (0.0)	2 (8.7)	1 (4.3)
Arm muscle area (AMA) categories					
Wasted	85 (60.7)	18 (62.1)	39 (78)	18 (60)	10 (32.3)
Below average	26 (18.6)	8 (27.6)	8 (16)	4 (13.3)	6 (19.4)
Average	26 (18.6)	2 (6.9)	2 (4)	8 (26.7)	14 (45.2)
Above average	3 (2.1)	1 (3.4)	1 (2)	0 (0.0)	1 (3.2)
High muscle	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

was almost two-third of the subject's requirement. The percent RDA of nutrient intake was demonstrated in Fig 3. Biochemical profile of subjects showed hyperglycemia in 25.5 % of subjects. Considering pre-transfusion hemoglobin (Hb), 100 % of subjects showed low Hb level which was less than 11.6 g/dl. Boys were more anemic compared to the girls. All of the subjects had high levels of serum ferritin. High level of T_4 was observed in 7.8 % of subjects, whilst low level of T_4 was present in 5.2 % of subjects.

There was a significant positive correlation ($P < 0.05$, $P < 0.01$) between the anthropometric parameters and the intake of energy and macronutrients. The intake of zinc and vitamin E was significantly ($P < 0.05$) correlated with increasing anthropometric parameters, especially weight and height, whereas the intake of vitamin D was negatively associated with anthropometric indices as shown in Table 3.

The Multiple Regression models predicting subjects' nutritional status was detailed in Table 4. In the predictive model for height, significant positive predictors of height included age, age at first transfusion, age of starting chelation and serum alkaline phosphatase. The significant negative predictors of height were gender and fasting blood sugar. Girls had shorter height compared to boys. In the predictive model for weight, age and serum alkaline phosphatase were positive predictors of weight. Puberty was the only negative predictor for weight. Pre-pubertal subjects had less weight compared to post-pubertal

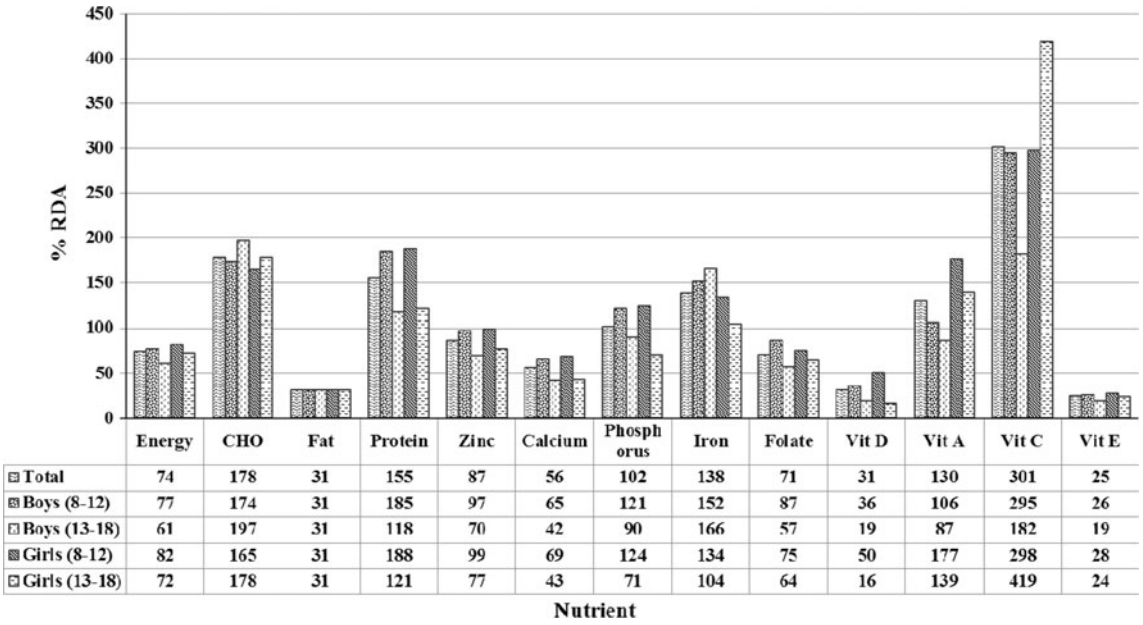

Fig. 3 Percentage of nutrient intake to RDAs (% RDA) according to gender and age

Table 3 Correlation coefficient between food intake and anthropometric parameters

Variable	Height	Weight	Triceps	AMA	Sub scapular[#]	MUAC	WC	BMI
Energy	0.64**	0.64**	0.22	0.56**	0.16	0.54**	0.55**	0.42**
Protein	0.36*	0.35*	0.12	0.26	0.09	0.25	0.25	0.19
Fat	0.35*	0.40**	0.27	0.35*	0.28	0.39*	0.40**	0.36*
CHO	0.49**	0.45**	0.30	0.42**	−0.06	0.35*	0.35*	0.22
Zinc	0.37*	0.38*	0.20	0.30	0.16	0.32*	0.32*	0.29
Copper	0.17	0.28	0.29	0.26	0.36*	0.31*	0.27	0.31
Calcium	−0.09	−0.05	0.08	−0.07	0.02	−0.02	−0.01	0.12
Phosphorus	0.17	0.24	0.14	0.22	0.21	0.23	0.25	0.33*
Iron	0.42**	0.45**	−0.002	0.33*	0.02	0.26	0.31*	0.20
Folate	0.15	0.16	−0.009	0.12	0.02	0.10	0.15	0.16
Vit B_{12}	0.04	0.11	0.21	0.12	0.22	0.16	0.10	0.12
Vit A	0.06	0.14	0.25	0.17	0.22	0.21	0.14	0.16
Vit C	0.14	0.22	0.28	0.12	0.20	0.23	0.22	0.29
Vit E	0.28	0.35*	0.38*	0.27	0.37*	0.37*	0.50**	0.41**
Vit D[#]	−0.35*	−0.36*	−0.10	−0.33*	−0.17	−0.29	−0.35*	−0.18
Selenium	0.25	0.19	−0.11	0.24	−0.07	0.12	0.13	−0.01

* $P < 0.05$, ** $P < 0.01$ significant level

[#] Spearman correlation

patients. For BMI, age acted as a positive predictor. The older subjects showed higher BMI.

Discussion

Malnutrition was detected in 57 and 60.7 % of the boys and girls, respectively, according to the height-for-age, as well as 82 and 70.6 % of boys and girls, respectively, according to the weight-for-age. Considering BMI, underweight was found in 44.3 % of boys and 19.6 % of girls. These results were similar to previous studies in different countries which showed high prevalence of impaired growth among children and adolescents suffering from transfusion-dependent β thalassemia [6, 7, 13, 14]. The prevalence of underweight in this study was higher (33.6 %) compared to

Table 4 Multivariate regression model predicting subject's nutritional status

Independent variables	Coefficient (B)	SE	*P* value
Model 1 ($R^2 = 0.33$, $F = 39.88$, $P < 0.001$); Outcome = BMI			
Age	0.37	0.06	<0.001
Model 2 ($R^2 = 0.71$, $F = 264.5$, $P < 0.001$); Outcome = Weight			
Puberty	(−) 7.07	1.8	<0.001
Age	2.14	0.17	<0.001
Serum ALP	0.007	0.003	0.026
Model 3 ($R^2 = 0.81$, $F = 376.4$, $P < 0.001$); Outcome = Height			
Age	3.43	0.18	<0.001
Age of 1st transfuse	0.07	0.02	0.011
Age chelation start	0.04	0.02	0.045
Serum ALP	0.008	0.004	0.028
FBS	(−) 0.03	0.01	0.013
Gender	(−) 3.32	1.35	0.016

Model 1 adjusted for; puberty, gender, serum Hb, serum Zn, serum vit D

Model 2 adjusted for; gender, serum calcium, FBS

Model 3 adjusted for; age of diagnosis, puberty

Puberty (1 = post-pubertal/0 = pre-pubertal), Gender (1 = boys/0 = girls)

BMI body mass index, *MUAC* mid upper arm circumference, *AMA* arm muscle area, *WC* waist circumference, *SE* standard error

Indian children in Pemde study [7] and Arab children in Nassar study [15] which was 23.8 and 20.6 %, respectively. This difference may be related to irregular iron chelation therapy which was shown in 15 % of subjects, as well as family income of which 65 % of subjects in this study belonged to poor income families.

Short stature was shown in 41 % of subjects and this was more common among boys (44.3 %) compared to girls (37.7 %). Similar studies in Iran and India have demonstrated higher prevalence of short stature, 69 and 63 % among Iranian thalassemic boys and girls and 57 % in Indian subjects, respectively [5, 16]. Other studies also showed almost similar result for short stature incidence among thalassemic children and adolescents, 33.1 [7], 36 [17] and 39.3 % [18]. Sum of triceps and subscapular skinfold thickness showed that 7.4 % of subjects were lean, accompanying 18.5 % as below average. Calculating AMA, 60.7 % of study subjects were wasted. The energy intake of subjects was only 74 % of RDA. These results were consistent with other researches that showed high prevalence of leanness and muscle wasting, as well as low energy intake among thalassemic children and adolescents [14, 19].

The intake of energy, macronutrients and iron was positively correlated with all anthropometric parameters in this study. The intake of zinc and vitamin E was significantly related to nutritional status of subjects via weight and height increment. The antioxidant effect of zinc and vitamin E may play an important role in nutritional status improvement by reducing the oxidative stress and resulting damage in different organs in thalassemia [20, 21]. The intake of vitamin D was negatively related to all anthropometric parameters. The negative association between vitamin D status and anthropometric parameters, especially BMI, WC and skinfold thickness was reported in earlier studies [22–24]. The other issue is that, as almost 85 % of subjects in this study were low in vitamin D status, these results are neither generalizable nor can be compared to other studies. It should be borne in mind that the cut-off point used, derived from western populations, may not be suitable for the Asian children such as in this study.

This study identified several factors predicting nutritional status in thalassemic children and adolescents. Older age, age at first transfusion, age of starting chelation and higher level of serum alkaline phosphatase were positive predictors of nutritional status, whereas female gender, prepubertal status and fasting blood sugar were negative predictors for height, weight and BMI, respectively. These results were in agreement with those who reported age and chelation characteristics as significant independent correlate for nutritional status of thalassemic patients [25].

Conclusion

The results of this study show that malnutrition, especially short stature and muscle wasting, is prevalent in thalassemic children and adolescent. Nutritional status of thalassemic patients is in significant correlation with their nutrient intake, focusing on zinc and vitamin E among micronutrients. Age of starting chelation therapy and the age of first transfusion for patients predict the nutritional status of thalassemic patients. Higher level of blood sugar can be a negative predictor for thalassemic children growth, so monitoring their blood glucose may improve their nutritional status. Therefore, nutritional interventions and nutrition education may play important roles in enhancing the quality of life in thalassemic children and adolescents.

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Conflict of interest None.

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