Acta Biomed 2023; Vol. 94, N. 3: e2023187 DOI: 10.23750/abm.v94i3.14732

Review

Nutritional studies in patients with β-thalassemia major: A short review

Ashraf Soliman [1], Mohamed Yassin [2], Fawzia Alyafei [1], Nada Alaaraj [1], Noor Hamed [1], Shayma Osman [1], Nada Soliman [3]

[1]Department of Pediatrics, Hamad General Hospital, Hamad Medical Center (HMC), Doha, Qatar; [2]National Centre Care and Research, Hamad Medical Corporation (HMC), [3]Department of Public Health, North Dakota State University (NDSU), ND, USA.

Abstract. *Background:* Patients with β-thalassemia major (BTM) had variable prevalence of undernutrition and abnormal body composition. *Methods:* We performed an electronic search in PubMed, Scopus, Research gate, and Web of Sciences to evaluate the prevalence of nutritional disorders in patients with BTM worldwide in relation to their body composition and possible etiological factors. In addition, we reviewed the published nutritional intervention studies. *Results:* 22 studies on the prevalence of undernutrition (12 countries) and 23 nutritional intervention studies were analyzed. Undernutrition occurred in a considerable number of patients but varied greatly among different countries (from 5.2% to 70%). The lower middle income (LMI) countries (India, Pakistan, Iran, Egypt) had higher prevalence, while (high -middle and high income (Turkey, Greece, North America, USA, Canada) had lower prevalence. Even in patients with normal BMI, abnormalities of body composition are common with decreased muscle mass, lean-body mass, and bone mineral density. 65% to 75% of them had lower energy intake with low levels of circulating nutrients, minerals (zinc, selenium, and copper), and vitamins (D, E) versus controls. Increased macro and micronutrient requirements decreased absorption and /or increased loss or excretion are etiologic factors. Undernutrition was associated with short stature and lower quality of life (QOL). High prevalence of endocrinopathies, poor transfusion regimen (tissue hypoxia), improper chelation, and lack of maternal education, represented important risk factors in the production of poor growth in weight and stature. *Conclusions:* Timely detection of undernutrition in patients with BTM and proper nutritional intervention could prevent growth delay and comorbidities. (www.actabiomedica.it)

Key words: β-thalassemia, undernutrition, underweight, body composition, prevalence, macronutrients, macronutrients**.**

Introduction

Nutritional status is important for growth, immune function, bone health and pubertal development. Patients with β-thalassemia major (BTM) suffer from several patterns of growth retardation including short stature, underweight, wasting, and decreased bone density. Previous reports suggested that nutritional factors play an important role in the etiology of their faltered growth (1,2).

The definition of optimum nutritional provision in thalassemic patients and how to provide it remain indefinable. In β-TM, the negative effect of impaired nutrition on growth intermingles with many other factors including chronic anemia, iron overload, and endocrine disorders. Overall, only a few well-designed

studies examined the causes, treatment, and prevention of common comorbidities and quality of life in thalassemic patients in relation to dietary and/or specific macro- and micronutrients. A few short-term studies investigated the effects of interventions on nutritional deficiencies in children with BTM and reported some beneficial effects on linear growth and bone health. However, the long-term advantages of these interventions still need to be evaluated (3,4).

Inadequate nutritional intake due to decreased appetite and fatigue secondary to anemia, increased energy expenditure (hypermetabolism) due to hyperactivity of bone marrow, tachycardia, increased respiratory rate, and gastrointestinal disturbances that can induce anorexia and diminished foods digestion and absorption, reduction of functions of the liver, secondary to liver siderosis, dysglycemia (insulin resistance and/or deficiency) and decreased insulin-like growth factor 1 (IGF-1). In addition, the high oxidative injury associated with iron overload can decrease anabolism and increase catabolism in these patients (5-7).

Moreover, many studies have reported decreased circulating levels of essential amino acids, vitamins and minerals compared to the normal population which advocates that thalassemia patients may probably require higher requirements and supplements (8,9).

Body composition is affected by many factors including nutrition, age, sex, endocrine system status, and the level of activity (exercise), but there are limited published data regarding the body composition status in this population, especially during adulthood. Lean tissue mass has been shown to be highly correlated with bone mineral density until the middle age when fat mass begins to account for a larger variance thereafter (10,11).

Aims of the review

To evaluate the prevalence of nutritional disorders (underweight and wasting) in patients with BTM worldwide in relation to their body composition and investigate the potential mechanisms that may contribute to undernutrition and disturbed body composition in these including the intake of macro and micronutrients.

Patients and Methods

We performed an electronic search in PubMed, Scopus, Research Gate, and Web of Sciences to evaluate the worldwide prevalence of nutritional disorders (underweight and wasting) in β-TM patients in relation to their body composition, and nutritional assessment including intake of macro and micronutrients. We used the following words in our search: Thalassemia Major, and Weight, and body mass index (BMI), and Underweight, And Malnutrition, And Wasting, and Body Composition, And Food Intake, And Macronutrients, And, Micronutrients, And Calories, And Protein, And Iron, And Ferritin, And Zinc, And Vitamins (D, E, C) and L-Carnitine, And Dietary Intervention. We focused on and reviewed the relationships between nutritional status and other comorbidities, in particular the low bone mass, growth deficiency, and endocrinopathies.

Inclusion criteria: papers [cross-sectional (CS), longitudinal (LS), controlled and uncontrolled, reviews and metanalysis] that studied patients with BTM, anthropometry, body composition, nutritional and dietary assessment, macro, and micronutrients between 1995 and 2022 were included.

Exclusion criteria: studies on other forms of hemoglobinopathies and those unrelated to the inclusion criteria or published before 1995 and those not written in English were excluded.

Three reviewers did the search separately and the selected manuscripts were pooled and reviewed by the 2 main authors after removing the duplicates. The NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to decide about the quality of the research papers. The important findings related to the review were extracted, tabulated, and analyzed.

Results

Twenty-three studies (n = 6561 children, adolescents and young adults with β-TM) published between 1995 and 2022, from USA, UK, Greece, Turkey, Iran, Egypt, Iraq, India, Pakistan, Bangladesh, Thailand,

and Malesia were included and analyzed for the following points:

1. Prevalence of underweight, wasting, and low BMI.
2. Abnormal body composition.
3. Different macro and micronutrients deficiencies; and
4. Different mechanisms are involved in the production of undernutrition.

In addition, 23 studies on different nutritional intervention in patients with BTM were included and analyzed for the possible effects of nutritional intervention on growth, bones, and general health. The PRISMA process was followed for the selection of papers (Figure 1).

Summary of the nutritional studies in BTM is presented in Table 1.

The following information were extracted from our research review:

1. Undernutrition occurred in a considerable number of patients with BTM, especially during childhood and adolescence.

   The prevalence varied greatly among different countries (from 5.2% to 74.5%). This great variability can be explained by the income/nutritional status of each country. The developing (lower middle-income countries: India, Pakistan, Iran, Egypt) had the higher prevalence versus (high -middle and high

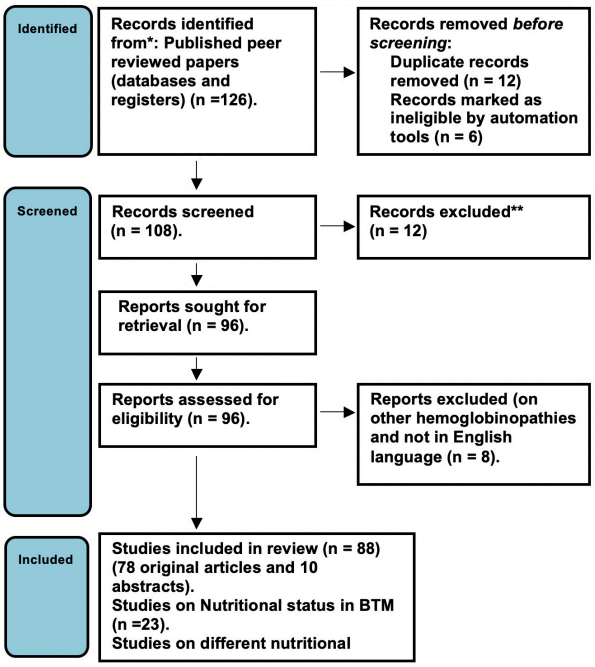

Figure 1 Identification of studies via literature search

Table 1. Nutritional studies in β-thalassemia major (BTM)

Study Author Year and Reference	Number Age Country Type of study	Percent of low body mass index (BMI)	Free mass index (FFM/FFMI) Fat mass (FM) Bone mass	Vitamin and mineral deficiencies
Lidoriki et al. Cureus.2022;14(8): e27985.(12)	67 patients Adults Greece CS	Low BMI < 5th centile =34.3%	Patients with low BMI: 86.6% had a low fat-free mass index (FFMI) and 74.6% had a high-fat mass (FM) index	92.2% Vitamin D deficiency (VDD).
Fung EB et al. J Acad Nutr Diet. 2012; 112 (7): 980-90. (13)	221 patients 19.7±11.3 yrs. 106 females USA CS	ND	ND	30% consumed inadequate levels of vitamin A, D, E, K, folate, calcium and magnesium. 61% had Vitamin D insufficiency (VDI).
Claster S, et al. Am J Hematol.2009;84 (6):344-8. (14)	24 patients 1.5 -31.4 yrs. USA CS	ND	ND	40–75% were deficient in A, C, D and selenium. 28–38% had low levels of B vitamins and folate.
Fung EB, et al. J Pediatr. 2010;157 (4):641-7. (15)	257 patients 23.7 ± 11 yrs. 51% male USA CS	BMI-Z score: < -2 5.2 % of 136 adults and 7.8 % of 115 children	Low bone mass, Adults 52.1% Children 43.4%.	

Table 1. Nutritional studies in β-thalassemia major (BTM)

Study Author Year and Reference	Number Age Country Type of study	Percent of low body mass index (BMI)	Free mass index (FFM/FFMI) Fat mass (FM) Bone mass	Vitamin and mineral deficiencies
Vogiatzi MG, et al. Br J Haematol. 2009;146(5):546-56. (16)	361 patients 49% male (6.1- 75 yrs. North America CS	Height-SDS < -2 SD = 25%	ND	12% VDD and 82% VDI.
Bulgurcu SC, et al. Medeni Med J. 2021;36(4):325-32. (17)	29 patients 12.2±4.7 yrs. Turkey CS	BMI< 5th centile = 31% Height <5th centile= 24.5%	ND	Hypomagnesemia in 3.5%, decreased ceruloplasmin in 10.3% and hypocalcemia in 17.2%.
Moiz B, et al. Hematology.2018; 23(4):248-52. (18)	367 children 10.6 ±3.3 yrs. Pakistan CS	BMI -Z score <- 2 SD =42% Height-SDS: < -< 2 = 65.4%	ND	ND
Biswas B, et al. Korean J Fam Med. 2021 ;42(1):66-72.(19)	328 children NR India CS	BMI -Z score <- 2 SD = 48.2%	ND	ND
Tienboon P, et al. Southeast Asian J Trop Med Public Health.1996 ;27 (2):356-61. (20)	115 children (61 girls) NR Thailand CS	Weight for age SDS (WAZ) < -2 Males: 64% Females:78 %	ND	ND
Shaidaton N, et al. Tech Nutr Food. Sci.2020 5(2). (21)	110 patients 18-40 yrs. Bangladesh CS	BMI: < 3rd centile = 62.4%	25% had poor food consumption, 32.5% consumed borderline food diet and only 6.7% of patients consumed acceptable high food diet.	Only 8.7% of patients consumed highly diversified food.
Vlychou M, et al. Int J Endocrinol. 2016;6218437. (22)	62 patients Mean age 36.4 yrs. Greece CS- controlled	BMI was lower in males vs. controls	Whole body lean mass and bone mineral density were lower in both male and female adult patients compared to controls.	ND
Asadi-Pooya AA, et al. Turk J Haematol. 2004 ;21(4):177-80. (23)	565 patients < 18 yrs. Turkey CS	BMI: < 10th centile = 12.4% < 10 yrs of age and = 46.5% > 10 yrs of age	ND	ND
Prakash A and Aggarwal R. North Am J Med Sci 2012; 4:141-4. (24)	19 adults >18 yrs. India CS	BMI: < 3rd centile = 42.1%	ND	ND
Seikh M A, et al. PJMHS. 2017; 11 (1). (25)	Three age groups: from 2-16 years (305 patients). Pakistan CS	In age group 2-6 yrs, underweight = 51.24% In age group 7-11 years = 56.45%	ND	

Table 1. Nutritional studies in β-thalassemia major (BTM)

Study Author Year and Reference	Number Age Country Type of study	Percent of low body mass index (BMI)	Free mass index (FFM/FFMI) Fat mass (FM) Bone mass	Vitamin and mineral deficiencies
Mahmoud RA, et al. Ital J Pediatr. 2021;47(1):165. (26)	120 children with BTM < 12yr Egypt CS	BMI- Z score: <-2 = 70%	ND	
Farmaki K, et al. Br J Haematol. 2010;148(3):466-75. (27)	52 patients with BTM LS	Significant increase BMI after chelation therapy	ND	
Badfar G, et al. Iran J Ped Hematol Oncol. 2017;7(4)245-59. (28)	Metanalysis 18 studies: 2,446 BTM Iran	Prevalence of underweight = 47.6% Delayed puberty: 67.5% Short stature: 52.3%	ND	
Shahar S, et al. Mediterr J Nutr Metab. 2013: 6: 45–51. (29)	140 BTM 8–18 yrs. Mashhad, Iran, CS	BMI-Z score: < -2 = 44.3 % for boys and 19.6 % for girls Height-SDS: < -2 = 44.3 % of boys and 37.7 % of girls	Sum of triceps and subscapular skinfold thickness and arm muscle area (AMA): 7.4 % leanness and 60.7 % wasting. The average of energy intake met 74 % of recommended dietary allowance.	The intake of energy, macronutrients, zinc, iron and vitamin E was positively correlated with anthropometric measurements.
Pemde H, et al. Pediatr Health Med Ther. 2011; 2:13-9. (30)	154 BTM 9.19 yrs. India CS	BMI-SDS: < -2 = 13%, and BMI-SDS: < -3 = 10.82% Height-SDS: < -2 = 33.1%	ND	
Nasr MR, et al. Egypt J Food Sci. 2003;31 (1-2):227-36. (31)	63 2-18 yrs. Egypt CS	BMI- Z score: < -2 =20%, Height-SDS: < -2 = 33%.		Serum levels of alpha-tocopherol, retinol and zinc, selenium, and copper levels were significantly decreased among BTM vs. controls.
Voravarn S, et al, Asia Pacific J Clin Nutr 1995, 4:133-5. (32)	47 children 4-5 yrs. Thailand CS	WAZ: <-2 = 74.5%, small muscle arm circumference= 75%	Children were receiving only 65% of the recommended energy intake for age	Hb level correlated with weight for age. Zinc deficiency correlated with linear growth
Yousefian S, et al. Iran J Ped Hematol Oncol. 2022;12(1)34-40. (33)	740 14 ±38 yrs. Iran CS	60.4% had BMI < 5th percentile	ND	A negative relation between BMI percentile and mean serum ferritin level
Saad H, et al. Farmacol Terapéut.2021;40, 5.8-0264.(34)	163 12.6 ±3.5 yrs. Iraq CS	Height- SDS: < -2 = 36.2%	ND	Significant correlation between BMI, Height- SDS and ferritin levels

Legend: CS = cross sectional, LS = longitudinal study, ND = not reported, WAZ: weight-for-age.

income) Turkey, Greece, North America, USA, Canada.
2. Even in patients with normal BMI, abnormalities of body composition were documented with decreased muscle mass, lean-body mass, and BMD, while the fat mass was variable.
3. Many thalassemic patients who described normal dietary intake had low levels of circulating nutrients, that may signify nutrient excretion or loss, or higher micronutrient requirements.
4. The energy intake met 65% to 75% of the recommended dietary allowance.
5. There was a high prevalence of decreased blood levels of vitamin D, alpha-tocopherol, retinol, zinc, selenium, and copper levels in BTM patients versus controls.
6. Decreased BMI was associated with short stature in a relevant number of patients (nutritional stunting).

Potential mechanisms that contribute to undernutrition and disturbed body composition in patients with β-TM.

The pathogenesis of poor weight gain, low BMI and disturbed body composition appears to be multifactorial and is mainly due to nutritional deficiency (macro and micronutrients), chronic anemia and hypoxia, iron overload of different organs, inadequate use of chelating agents, and endocrinopathies (hypogonadism, delayed puberty, hypothyroidism, and GH-IGF-1 axis deregulations (Figure 2).

Decreased intake and increased loss of macro and micronutrients.

Few studies have specifically focused on aspects of nutritional status and health in patients with β-TM. Most of the published work has summarized observations in small numbers of subjects primarily conducted outside North America (35-39).

In many studies, the intake of energy, macronutrients, and micronutrients (zinc, vitamin D, selenium, chromium, alpha tocopherol, and vitamin E) have been shown to be correlated with all anthropometric parameters of BTM patients. The antioxidant effect of zinc and vitamin E have been suggested to play a significant role in maintaining good nutritional status by reducing the oxidative stress (induced by iron overload) that causes damage in different organs. The decreased intake of vitamin D was negatively related to all anthropometric parameters. In addition, the association between low vitamin D status and decreased

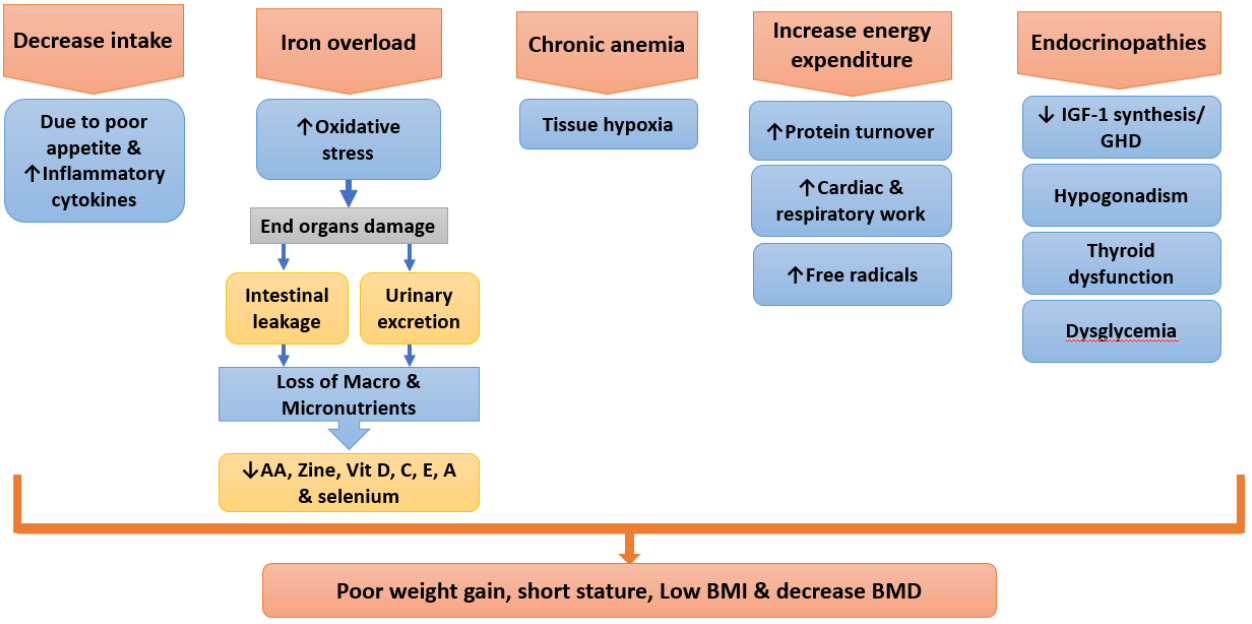

Figure 2. Potential mechanisms that contribute to malnutrition and abnormal body composition in BTM. Legend: AA= amino acids, Vit = vitamin, GHD = growth hormone deficiency

growth [BMI, weight-for-age (WAZ) and skinfold thickness] was reported in several studies (40-44).

Goldberg et al. (45), reviewed 97 studies on nutrition in BTM patients. The authors reported that patients with BTM frequently had deficiencies in vitamins A, C, D, selenium, and zinc. The prevalence of these nutritional deficiencies was positively associated with age and iron overload. Evidence to support the role of vitamin D and zinc for bone health was observed. Zinc was found to improve glucose metabolism and bone mineral density. Authors recommended routine supplementation with vitamin D and zinc. In addition to decreased intake of micronutrients, increased loss of some minerals has been found in BTM due to chelation therapy. Increased urinary zinc excretion has also been reported in these patients (46).

A significant decrease in intestinal calcium transport has been reported in thalassemic patients. Generally, iron hyperabsorption in these patients leads to impaired calcium absorption. Negative correlation between iron and calcium transport has been demonstrated in the duodenum of thalassemic mice (47,48).

In addition, iron overload has been shown to induce intestinal leakage, gut translocation of organismal molecules, and reshapes gut microflora. These changes can adversely affect absorption, energy metabolism and immune function in patients with thalassemia (49-52).

Abdulrazzaq, et al. (53), reported lower plasma values of essential amino acids and a decrease in urinary amino acids in BTM patients compared to normal controls.

Increased energy expenditure in BTM patients

Vaisman et al. (54) reported that in thalassemic patients (n = 7, age 22-30 years) the resting energy expenditure (REE) was greater before blood transfusion in absolute numbers and as a percentage of the predicted value. REE returned to normal range after blood transfusion (6138 ±112 vs. 5678 ± 738 kJ.kg-1. d-1 and 111.7 ± 11.3% vs. 103.2 ±7.8%, respectively). Protein contribution to REE was (9.7 ± 4.2%) before blood transfusion and increased to (15.3 ± 5.2%) after transfusion. They proposed that increased protein turnover and increased cardiac work contributed to the observed increase in REE (54).

The increased oxidative stress in BTM patients was due to iron overload and unstable hemoglobin together stimulate the production of excess free radicals. Malondialdehyde (MDA), a product of lipid peroxidation and protein carbonyls, representing oxidation of the circulating proteins, is elevated in BTM. This marker is correlated with elevated REE (55-57).

Intervention studies performed to increase caloric intake in children with BTM proved that high caloric diet had significantly increased IGF-I levels, BMI, mid-arm circumference and skin fold thickness (37,38).

Iron overload (serum ferritin and BMI) and chelation therapy

In BTM *patients* multiple blood transfusions, ineffective erythropoiesis and upregulated iron absorption from the gastrointestinal system led to iron overload in the body. This secondary hemosiderosis has a deleterious effect on their different body organs, including heart, liver, and endocrine system. Serum ferritin is a commonly used marker of iron status in BTM patients. In 2 large cohorts of thalassemic children and adolescents in Iran (n= 740) and Iraq (n = 165) a negative relationship has been recognized between the BMI percentile and mean serum ferritin levels (58).

Intensive/effective chelation therapy has been shown to prevent or reduce iron accumulation and iron-mediated organ damage, resulting in a consistent decrease in the rate of new endocrine disorders. Poor chelation increased the risk of developing growth and pubertal disorders and glucose homeostasis that affect body composition status (59-62).

Blood transfusion and level of hemoglobin (correction of anemia) in relation to BMI and nutrition

Chronic anemia and low Hb level markedly affect growth in children with BTM. One of the criteria to start transfusion in infants with BTM (<2 years) is failure to gain weight for 3 months without another etiology (63).

Patients with non-transfusion dependent thalassemia had significantly lower BMI compared to those on regular transfusion (higher Hb). In addition,

hemoglobin level has been positively correlated to lean mass (P=0.008). This effect of increased Hb on weight gain can be achieved through improving the appetite, increasing oxygen supply to the growing organs, and increasing IGF-1 secretion (64-67).

Endocrinopathies in BTM patients, effect on weight gain, BMI, and body composition

Decreased IGF-1 secretion with or without growth hormone deficiency (GHD) is common in children and adolescents with BTM especially those with slow growth and pubertal delay. Although GHD can explain in part the low IGF-I synthesis, many other factors contribute to this decreased synthesis of IGF-I including decreased nutritional intake (macronutrients, zinc, vitamin D), severe anemia, hepatic dysfunction, thyroid dysfunction and delayed or absent puberty (hypogonadism) (3, 68-70).

During pubertal development, significant positive correlations exist between IGF-1 and testosterone, IGF-1 and estradiol serum concentrations as well as between IGF-1 serum concentration, BMI and sum of skin folds thicknesses. The interactions between GH-IGF-1 and sex steroids (especially androgens) express an anabolic effect on muscle mass, bone mineralization and body proportion which constitutes the male and the female adult body composition. From early pubertal stage until late puberty, IGF-I levels correlate directly with weight, BMI, height, and fat free mass (FFM) in pre-pubertal girls, but these by late puberty. The lean body mass (LBM) and the mean bone mineral content (BMC) for age and bone area (BA) for age Z-score is greater in children with higher IGF-1 Z-score versus those with lower IGF-1 Z-score. IGF-1, height, the sex steroids, and Tanner stages, rises steeply in individuals during puberty, with the timings of the rises tightly synchronized within individuals (71-76).

IGF-1 is a major regulator of muscle mass during development, thanks to its effect on myogenic cell proliferation and differentiation. As to the role of IGF-1 in adult skeletal muscle, several studies indicate that IGF-1 can induce hypertrophy and block atrophy (77).

Sex steroids influence the maintenance and growth of muscles. Decline in androgens, estrogens, and progesterone by aging leads to the loss of muscular function and mass, sarcopenia. These steroid hormones can interact with different signaling pathways through their receptors (78).

In BTM patients, the common occurrence of delayed and/or failure of puberty due to hypo gonadotropic hypogonadism with or without gonadal dysfunction and low IGF-1 secretion can negatively impact growth (weight and height) and body composition via the modulation of cellular response to IGF-1. This can explain the loss and/or attenuation of pubertal growth spurt (weight and height) and abnormalities of body composition and decreased bone mineral density in BTM patients (79,80).

In addition, low leptin and high ghrelin levels have been described in patients with BTM. A significant correlation was observed between BMI and leptin in two studies (81-84).

Effect of undernutrition on Quality of Life (QoL) in patients with BTM

In an Indian analytical observational study among 328 BTM children attending the thalassemia day care unit, 48.2% were malnourished with a mean body mass index of 13.9 kg/m^2. Malnutrition negatively impacted total QoL and various domains of the study participants (85). Two other studies from Egypt, on 67 and 64 BTM children and adolescents reported that the QOL improved with attaining higher weight percentile, Hb > 8 g/dL and decreasing serum ferritin <1,500 ng/ml (86,87).

Nutritional intervention studies in patients with BTM

Patients with thalassemia have a high prevalence of malnutrition, underweight and low BMI. They had low circulating levels of many nutrients, but the nutritional intervention (NI) studies were scarce. Two NI studies investigated the effect/s of increasing mean energy intake by 20 and 30-50%, respectively, in 12 and 15 children with β-TM for 4 and 8 weeks, respectively. Authors reported significant increase in body weight, BMI, fat-free mass, fat mass and accelerated height velocity associated with increased IGF-1 (38). On the other hand, NI using micronutrients discovered variable clinical and biochemical effects. One controlled

study proved that zinc (Zn) supplementation for 18 months increased serum Zn and bone mineral content of patients with BTM (n = 40) versus controls (88). Longer term-controlled trial using Zn supplementation (n = 32 patients, aged 1-7 years) increased linear growth compared to thalassemic children without Zn supplementation (89).

A study on 64 patients found that Zn supplements reduced anti-heat shock protein (anti-HSP27) titers in patients with BTM suggesting a potential antioxidant and anti-inflammatory effects. Another placebo-controlled study (n = 120) showed that supplementations of Zn and vitamin E, increased BMI, superoxide dismutase (SOD), glutathione peroxidase (GPX) and total antioxidant capacity (TAC) (90,91).

In 3 nutritional intervention (NI) studies, vitamin E supplementation for 1- 9 months improved the antioxidant/ oxidant balance in plasma and red blood cells, counteracted lipid peroxidation processes and increased red blood cells membrane fluidity (92-94). In one study, daily vitamin C supplementation for a year potentiated the efficacy of DFO to reduce iron overload (95).

Vitamin D supplementation studies (intermittent mega dose, orally or IM, or daily oral dose) indicated increased serum 25-OHD level and significant improvement of symptoms related to vitamin D deficiency in adolescents with BTM (96-98) . In one study on 30 children with BTM, oral vitamin D and calcium supplementation for 1-year increased BMC (99).

Oral supplementation of L-carnitine for 1 month decreased lipid peroxidation and improved RBC deformability while supplementation for 6 months improved pubertal development, cardiac performance, and physical fitness and in BTM adolescents (100-103).

In another RCT study, folate supplementation for 3 months in children with β -thalassemia minor, but not BTM β-TM increased hemoglobin levels and decreased symptoms of bone pain fatigue and myalgia. However, one study suggested a positive role of folic acid in preventing progression of arteriosclerosis and decreasing thromboembolic events (104-106).

Based on these data and others a recent review of nutritional deficiencies, in relation to morbidity, suggested a moderate useful evidence of supplementing vitamin D, vitamin E, zinc and vitamin C in thalassemic patients (45).

Suggested Diet and food items suitable for patients with BTM:

Because of the variable degree of iron overload in BMT patients as well as their increased gut absorption of iron they can be advised to consume low-iron foods that satisfy their age and sex recommended intake of macro and micronutrients.

A) Foods suggested to encourage:

1. Fruits and vegetables: Green leafy vegetables have good antioxidant properties that inhibit free radical production. Although some vegetables and fruits contain oxalates, which impairs non-heme iron absorption: kale, rhubarb, spinach, and strawberries. In addition, apples, artichokes, Berries, plums, sweet cherries, chicory, and red onions contain polyphenols. which impairs heme iron absorption (107,108).

2. Lean protein, eggs, and dairy foods: Lean protein with relatively lower iron content compared to red meat like chicken, white-meat turkey, cod, mackerel, and salmon can be used to satisfy the recommended intake of proteins. Eggs contain Phosvitin, a phosphoprotein which binds to iron and helps limit the amount of iron the body absorbs, and egg white is a high-quality protein. Egg protein has been demonstrated to be important to skeletal muscle health and protective against sarcopenia. Dairy products like milk, yogurt, and white cheese, and are good source of protein and calcium and poor sources of iron that make them very useful in thalassemic patients (109,110).

3. Legumes, grains, nuts, seeds, and beans: Whole grains, legumes, seeds, beans, and some nuts contain phytates or phytic acid, which can decrease the absorption of iron. In addition, their high content of fiber decreases absorption of non-heme iron (111,112).

4. Tea: Drinking tea which contains tannins may impair iron bioavailability especially when taken with meals (113,114).

B) Foods suggested to avoid:

A low-iron diet for patients with BTM requires avoiding foods that are rich sources of heme iron,

which is more easily absorbed by the body. Here are some food and beverages to avoid or reduce in a low-iron diet:

1. Red meat in excess: A small amount of red meat may be acceptable but excess intake of red meat like beef that contains easily absorbed heme iron should be discussed with a healthcare provider or registered dietitian (115).

2. Alcoholic beverages: Alcoholic drinks can potentially cause injury to the liver in those people with hepatic iron overload. Therefore, avoiding or limiting it is advisable in thalassemic patients. In addition, those with cirrhosis secondary to iron overload must stop drinking alcohol (116).

3. Sugars : Food and beverages high in certain sugars (e.g., high fructose corn syrup, which is the major source of fructose in a Western diet) can increase absorption of non-heme iron 3 folds. Sucrose and glucose did not appear to increase the absorption of dietary iron. Wise use of simple sugars is advised in case of prediabetes and diabetes (117,118).

Conclusions

It can be concluded that in thalassemic children and adolescents have high prevalence of underweight, nutritional wasting, stunting and change of body composition and decreased bone mineral density. Reduced nutrient intake and/or increased energy expenditure contribute to these forms of malnutrition. The available nutritional intervention studies proved some success to increase growth in these children (vitamin D, E, C and zinc). Therefore, besides increasing Hb level and effective chelation therapy, nutritional support and follow up of nutritional status including weight gain, BMI, height velocity and bone health appear very important to maintain normal growth and good quality of life in these patients.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Ethic Permission: A review paper that does not require an institutional ethics approval.

Author Contributions: Conceptualization: AS; Data collection and analysis: AS, MY, F, NH; Writing original draft preparation: FA, SO, NH; Tabulation and figures: NA, NS; Revision of manuscript for important intellectual content and editing: AS, MY.

References

1. Fung EB. Nutritional deficiencies in patients with thalassemia. Ann N Y Acad Sci. 2010; 1202:188-96. doi: 10.1111/j.1749-6632.2010.05578. x.
2. Fucharoen S, Ketvichit P, Pootrakul P, et al, Clinical manifestation of beta-thalassemia/hemoglobin E disease. J Pediatr Hematol Oncol. 2000 ;22(6):552-7. doi: 10.1097/00043426-200011000-00022.
3. Soliman AT, De Sanctis V, Elalaily R, Yassin M. Insulin-like growth factor- I and factors affecting it in thalassemia major. Indian J Endocrinol Metab. 2015;19(2):245-51. doi: 10.4103/2230-8210.131750.
4. Fung EB, Xu Y, Trachtenberg F, et al. Thalassemia Clinical Research Network. Inadequate dietary intake in patients with thalassemia. J Acad Nutr Diet. 2012;112(7):980-90. doi: 10.1016/j.jand.2012.01.017.
5. Schnedl WJ, Schenk M, Lackner S, et al. β-thalassemia minor, carbohydrate malabsorption and histamine intolerance. J Community Hosp Intern Med Perspect. 2017;7(4):227-9. doi: 10.1080/ 20009666. 2017. 1369378.
6. Musallam KM, Taher AT, Cappellini MD, Sankaran VG. Clinical experience with fetal hemoglobin induction therapy in patients with β-thalassemia. Blood. 2013;121(12):2199-212. doi: 10.1182/blood-2012-10-408021.
7. Vlachos P, Liakakos D. Malabsorption of vitamin B12 in homozygous beta-thalassemia. Nuklearmedizin. 1976;15(4):195-6. PMID: 980798.
8. Goldberg EK, Neogi S, Lal A, Higa A, Fung E. Nutritional Deficiencies Are Common in Patients with Transfusion-Dependent Thalassemia and Associated with Iron Overload. J Food Nutr Res (Newark). 2018;6(10):674-681. doi: 10.12691/jfnr-6-10-9.
9. Fung EB. The importance of nutrition for health in patients with transfusion-dependent thalassemia. Ann N Y Acad Sci. 2016;1368(1):40-8. doi: 10.1111/nyas.13003.
10. Rosen C J, Klibanski A. Bone, fat, and body composition: evolving concepts in the pathogenesis of osteoporosis. Am J Med. 2009;122(5):409–14. doi: 10.1016/j.amjmed.2008.11.027.
11. 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. Am J Hematol. 2014;89(12):1102–6. doi: 10.1002/ajh.23844.
12. Lidoriki I, Stavrou G, Schizas D, et al . Nutritional Status in a Sample of Patients With β-Thalassemia Major. Cureus. 2022, 14;14(8):e27985. doi: 10.7759/cureus.27985.
13. Fung EB, Xu Y, Trachtenberg F, et al. Thalassemia Clinical Research Network. Inadequate dietary intake in patients with thalassemia. J Acad Nutr Diet. 2012,112(7):980-90.

doi: 10.1016/j.jand.2012.01.017.
14. Claster S, Wood JC, Noetzli L, Carson SM, et al. Nutritional deficiencies in iron overloaded patients with hemoglobinopathies. Am J Hematol. 2009 ;84(6):344-8. doi: 10.1002/ajh.21416.
15. Fung EB, Xu Y, Kwiatkowski JL, Vogiatzi MG, Neufeld E, Olivieri N, Vichinsky EP, Giardina PJ; Thalassemia Clinical Research Network. Relationship between chronic transfusion therapy and body composition in subjects with thalassemia. J Pediatr. 2010 Oct;157(4):641-7, 647.e1-2. doi: 10.1016/j.jpeds.2010.04.064.
16. Vogiatzi MG, Macklin EA, Trachtenberg FL, et al,. Thalassemia Clinical Research Network. Differences in the prevalence of growth, endocrine and vitamin D abnormalities among the various thalassaemia syndromes in North America. Br J Haematol. 2009;146(5):546-56. doi: 10.1111/j.1365-2141. 2009. 07793.x.
17. Bulgurcu SC, Canbolat Ayhan A, Emeksiz HC, et al. Assessment of the Nutritional Status, Bone Mineralization, and Anthropometrics of Children with Thalassemia Major. Medeni Med J. 2021 19;36(4):325-32. doi: 10.4274/MMJ.galenos.2021.66915.
18. Moiz B, Habib A, Sawani S, et al. Anthropometric measurements in children having transfusion-dependent beta thalassemia. Hematology. 2018;23(4):248-252. doi: 10.1080/10245332.2017.1396044.
19. Biswas B, Naskar NN, Basu K, et al. Malnutrition, Its Attributes, and Impact on Quality of Life: An Epidemiological Study among β-Thalassemia Major Children. Korean J Fam Med. 2021;42(1):66-72. doi: 10.4082/kjfm.19.0066.
20. Tienboon P, Sanguansermsri T, Fuchs GJ. Malnutrition and growth abnormalities in children with beta thalassemia major. Southeast Asian J Trop Med Public Health. 1996 ;27(2):356-61. PMID: 9280002.
21. Nisha S, Alam SS, Rahman Md.N, Islam K. Nutritional Status and Dietary Patterns of Thalassemia Patients at Selected Hospitals in Dhaka City, Bangladesh. Nov Tech Nutri Food Sci. 2020;5(2). NTNF. 000607. doi: 10.31031/NTNF.2020.05.000607.
22. Vlychou M, Alexiou E, Thriskos P, et al. Body Composition in Adult Patients with Thalassemia Major. Int J Endocrinol. 2016; 2016:6218437. doi: 10.1155/2016/6218437.
23. Asadi-Pooya AA, Karamifar H. Body mass index in children with beta-thalassemia major. Turk J Haematol. 2004;5;21(4):177-80. PMID: 27264281.
24. Prakash A, Aggarwal R. Thalassemia major in adults: short stature, hyperpigmentation, inadequate chelation, and transfusion-transmitted infections are key features. North Am J Med Sci 2012; 4:141-4. doi: 10.4103/1947-2714.93886.
25. Sheikh MA, Shakir MU, Shah M. The Assessment of Nutritional Status of Children with Beta Thalassemia Major with Body Mass Index. PJMHS. 2017:11 (1) 262-5.
26. Mahmoud RA, Khodeary A, Farhan MS. Detection of endocrine disorders in young children with multi-transfused thalassemia major. Ital J Pediatr. 2021:31;47(1):165. doi.org/10.1186/s13052-021-01116-2.
27. Farmaki K, Tzoumari I, Pappa C, et al. Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major. Br J Haematol. 2010;148(3):466-75. doi:10.1111/j.1365-2141.2009.07970.
28. Gholamreza B, Nasirkandy P, Masoumeh S et al. Prevalence of Short Stature, Underweight and Delayed Puberty in Iranian Patients with Thalassemia Major: A Systematic Review and Meta-Analysis. Iran J Ped Hematol Oncol. 2017:7(4): 245-59. doi:ijpho.ssu.ac.ir/article-1-338-en.html.
29. Shahar S, Ghayour-Mobarhan M, Mirhosseini NZ, et al. Factors affecting nutritional status among pediatric patients with transfusion-dependent beta thalassemia. Mediterr J Nutr Metab. 2013; 6:45–51 doi: 10.1007/s12349-012-0112-0.
30. Pemde H, Jagdish Chandra J, Gupta D, et al. Physical growth in children with transfusion-dependent thalassemia. Pediatric Health Med Ther. 2011; 2:13-9. doi.org/10.2147/PHMT.S15305.
31. Nasr MR, Ali S, El Gabry E. Malnutrition, and growth abnormalities among Egyptian children with beta-thalassemia major. Egyp J Food Sci. 2003; 31 (1-2): 227-36. https://pubmed.ncbi.nlm.nih.gov/9280002/
32. Voravarn S, Tanphaichitr MS, Visuthi B, Tanphaichitr V . Causes of inadequate protein-energy status in thalassemic children. Asia Pacific J Clin Nutr 1995; 4:133–135. https://pubmed.ncbi.nlm.nih.gov/24394268/
33. Yousefian S, Aliabad GM, Saleh R, Khedmati M. Association of Body mass index and serum ferritin level in pediatrics with Beta -thalassemia major disease. Iran J Ped Hematol Oncol. 2022;12 (1) 34-40. doi: ijpho.ssu.ac.ir/article-1-611-en.html.
34. Bash HS, Al-Hindy A, Al-Mamory BH, et al. The study of serum ferritin level as a predictor of growth retardation in Thalassemia-major. doi.org/10.5281/zenodo.5449803.
35. Filosa A, Di Maio S, Esposito G, et al. Persistence of delayed adrenarche in boys with thalassemia. J Pediatr Endocrinol. 2001; 14:407–14. doi.org/10.1515/JPEM.2001.14.4.407.
36. Tienboon P. Effect of nutrition support on immunity in paediatric patients with beta-thalassaemia major. Asia Pacific J Clin Nutr. 2003; 12:61–5. PMID: 12737012.
37. Fuchs GJ, Tienboon P, Linpisarn S, et al. Nutritional factors and thalassaemia major. Arch Dis Child. 1996;74(3):224-7. doi: 10.1136/adc.74.3.224.
38. Soliman AT, El-Matary W, Fattah MM, et al. The effect of high-calorie diet on nutritional parameters of children with beta-thalassaemia major. Clin Nutr. 2004; 23:1153–8. doi: 10.1016/j.clnu.2004.03.001.
39. Kalef-Ezra J, Zibis A, Chaliassos N, et al. Body composition in homozygous B-Thalassemia. Ann NY Acad Sci. 2000; 904:621–4. doi: 10.1111/j.1749-6632.2000.tb06527.
40. Mirhosseini, N. Z., Shahar, S, Ghayour-Mobarhan, M, et al. Factors affecting nutritional status among pediatric patients with transfusion-dependent beta thalassemia. Mediterr J Nutr Metab. 2013; 6:45–51 doi:10.1007/s12349-012-0112-0

41. Kassab-Chekir A, Laradi S, Ferchichi S, et al. Oxidant, antioxidant status and metabolic data in patients with beta thalassemia. Clin Chim Acta. 2003: 338:79–86. doi: 10.1016/j.cccn.2003.07.010.
42. Soliman AT, De Sanctis V, Elalaily R, et al. Vitamin D deficiency in adolescents. Indian J Endocrinol Metab. 2014;18 (Suppl 1):S9-S16. doi: 10.4103/2230-8210.145043.
43. Eshghi P, Alavi S, Ghavami S, Rashidi A. Growth impairment in β-thalassemia major: the role of trace element deficiency and other potential factors. J Pediatr Hematol Oncol.2007: 29:5–8. doi: 10.1097/ MPH. 0b013e31802d74f3.
44. Fung EB, Xu Y, Trachtenberg F, et al. Thalassemia Clinical Research Network. Inadequate dietary intake in patients with thalassemia. J Acad Nutr Diet. 2012;112(7):980-90. doi: 10.1016/j.jand.2012.01.017.
45. Goldberg EK, Lal A, Fung EB. Nutrition in Thalassemia: A Systematic Review of Deficiency, Relations to Morbidity, and Supplementation Recommendations. J Pediatr Hematol Oncol. 2022 ;44(1):1-11. doi: 10.1097/ MPH.0000000000002291.
46. Fung EB, Kwiatkowski JL, Huang JN, Gildengorin G, King JC, Vichinsky EP. Zinc supplementation improves bone density in patients with thalassemia: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2013;98(4):960-71. doi: 10.3945/ajcn.112.049221.
47. Liakakos D, Vlachos P, Anoussakis C, et al. Calcium metabolism in children suffering from homozygous β-thalassaemia after oral administration of 47Ca. Nuklearmedizin. 1976 15:77–9. PMID: 1272816.
48. Kraidith K, Svasti S, Teerapornpuntakit J, et al. 1,25(OH)2D3 effectively restore Ca2+ transport in β-thalassemic mice: reciprocal phenomenon of Fe2+ and Ca2+ absorption. Am J Physiol Endocrinol Metab.2016; 311:E214–E23. doi: 10.1152/ajpendo.00067.2016.
49. Mariani R, Trombini P, Pozzi M, Piperno A. Iron metabolism in thalassemia and sickle cell disease. Mediterr J Hematol Infect Dis. 2009;1(1). doi: 10.4084/MJHID.2009.006.
50. Visitchanakun P, Saisorn W, Wongphoom J, et al. Gut leakage enhances sepsis susceptibility in iron-overloaded β-thalassemia mice through macrophage hyperinflammatory responses. Am J Physiol Gastrointest Liver Physiol. 2020;318(5):G966-G9. doi: 10.1152/ajpgi.00337.2019.
51. Botta A, Barra NG, Lam NH, et al. Iron Reshapes the Gut Microbiome and Host Metabolism. J Lipid Atheroscler. 2021;10(2):160-83. doi: 10.12997/jla.2021.10.2.160.
52. Flint HJ, Scott KP, Louis P, Duncan SH. The role of the gut microbiota in nutrition and health. Nat Rev Gastroenterol Hepatol. 2012;9(10):577-89. doi: 10.1038/nrgastro.2012.156.
53. Abdulrazzaq YM, Ibrahim A, Al-Khayatb Al, et al. Beta-thalassemia major and its effect on amino acid metabolism and growth in patients in the United Arab Emirates. Clin Chim Acta. 2005; 352:183–90. doi: 10.1016/j.cccn.2004.09.017.
54. Vaisman N, Akivis A, Sthoeger D, Barak Y, Matitau A, Wolach B. Resting energy expenditure in patients with thalassemia major. Am J Clin Nutr. 1995;61(3):582-4. doi: 10.1093/ajcn/61.3.582.
55. Fibach E, Dana M. Oxidative Stress in β-Thalassemia. Mol Diagn Ther. 2019;23(2):245-61. doi: 10.1007/s40291-018-0373-5.
56. Walter PB, Fung EB, Killilea DW, et al. Oxidative stress and inflammation in iron-overloaded patients with beta-thalassaemia or sickle cell disease. Br J Haematol. 2006;135(2):254-63. doi: 10.1111/j.1365-2141.2006.06277.
57. Akohoue S, Shankar S, Milne G, et al. Energy Expenditure, Inflammation, and Oxidative Stress in Steady-State Adolescents With Sickle Cell Anemia. Pediatr Res.2007; 61;233–8. doi: 10.1203/ pdr. 0b013e31802d7754.
58. Yousefian S, Aliabad GM, Saleh R, Khedmati M. Association of Body mass index and serum ferritin level in pediatrics with Beta -thalassemia major disease. Iran J Ped Hematol Oncol. 2022;12 (1): 34-40. doi: ijpho.ssu.ac.ir/article-1-611-en._
59. De Sanctis V, Soliman AT, 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 J Endocrinol Metab. 2013;17(1):8-18. doi: 10.4103/2230-8210.107808.
60. 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. Am J Hematol. 2014;89(12):1102-6. doi: 10.1002/ajh.23844.
61. Farmaki K, Tzoumari I, Pappa C, et al. Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major. Br J Haematol. 2010;148(3):466-75. doi:10.1111/j.1365-2141.2009.07970.x.
62. Shalitin S, Carmi D, Weintrob N, et al. Serum ferritin level as a predictor of impaired growth and puberty in thalassemia major patients. Eur J Haematol. 2005 ;74(2):93-100. doi: 10.1111/j.1600-0609.2004.00371.
63. Lal A, Wong T, Keel S, et al. The transfusion management of beta thalassemia in the United States. Transfusion. 2021;61(10):3027-39. doi: 10.1111/trf.16640.
64. Ghrayeb H, Elias M, Nashashibi J, et al. Appetite and ghrelin levels in iron deficiency anemia and the effect of parenteral iron therapy: A longitudinal study. PLoS One. 2020;15(6):e0234209. doi: 10.1371/ journal.pone.0234209.
65. Mahachoklertwattana P, Yimsumruay T, Poomthavorn P, et al. Acute effects of blood transfusion on growth hormone and insulin-like growth factor-1 levels in children with thalassemia. Horm Res Paediatr. 2011;75(4):240-5. doi: 10.1159/000321189.
66. Soliman AT, Abushahin A, Abohezeima K, et al. Age related IGF-I changes and IGF-I generation in thalassemia major. Pediatr Endocrinol Rev. 2011;8 (Suppl 2):278-83. PMID: 21705978.
67. Soliman A, Yasin M, El-Awwa A, et al. Acute effects of blood transfusion on pituitary gonadal axis and sperm parameters in adolescents and young men with thalassemia major: a pilot study. Fertil Steril. 2012;98(3):638-43. doi:

10.1016/j.fertnstert.2012.05.047.
68. Veldhuis JD, Roemmich JN, Richmond EJ, et al. Endocrine control of body composition in infancy, childhood, and puberty. Endocr Rev. 2005;26(1):114-46. doi: 10.1210/er.2003-0038
69. Riza M, Mulatsih S, Triasih R. Factors associated with insulin-like growth factor-1 in children with thalassemia major.2019 ;59(2):72. doi.org/10.14238/pi59.2.2019.72-8.
70. Soliman AT, Khalafallah H, Ashour R. Growth and factors affecting it in thalassemia major. Hemoglobin. 2009;33 (Suppl 1):S116-26. doi: 10.3109/03630260903347781.
71. Kulik-Rechberger B, Janiszewska O. Insulin-like growth factor 1, its binding protein 3, and sex hormones in girls during puberty. Ann Univ Mariae Curie Sklodowska Med. 2004;59(2):75-9. PMID: 16146053.
72. Beckett PR, Wong WW, Copeland KC. Developmental changes in the relationship between IGF-I and body composition during puberty. Growth Horm IGF Res. 1998;8(4):283-8. doi: 10.1016/s1096-6374(98)80123-8.
73. Ekbote VH, Khadilkar VV, Khadilkar AV, et al. Relationship of insulin-like growth factor 1 and bone parameters in 7-15 years old apparently, healthy Indian children. Indian J Endocrinol Metab. 2015;19(6): 770-4. doi: 10.4103/2230-8210.167549.
74. Kanbur NO, Derman O, Kinik E. The relationships between pubertal development, IGF-1 axis, and bone formation in healthy adolescents. J Bone Miner Metab. 2005;23(1):76-83. doi: 10.1007/s00774-004-0544-9.
75. Cole TJ, Ahmed ML, Preece MA, Hindmarsh P, Dunger DB. The relationship between Insulin-like Growth Factor 1, sex steroids and timing of the pubertal growth spurt. Clin Endocrinol (Oxf). 2015 ; 82(6):862-9. doi: 10.1111/cen.12682.
76. Ong KK, Emmett P, Northstone K, et al. Infancy weight gain predicts childhood body fat and age at menarche in girls. J Clin Endocrinol Metab. 2009;94(5):1527-32. doi: 10.1007/s10995-012-1139-z.
77. Schiaffino S, Mammucari, C. Regulation of skeletal muscle growth by the IGF1-Akt/PKB pathway: insights from genetic models. Skeletal Muscle.2011;1:4. doi.org/10.1186/2044-5040-1-4.
78. Kim YJ, Tamadon A, Park HT, et al. The role of sex steroid hormones in the pathophysiology and treatment of sarcopenia. Osteoporos Sarcopenia. 2016;2(3):140-55. doi: 10.1016/j.afos.2016.06.002.
79. Gagliardi I, Mungari R, Gamberini MR. et al. GH/IGF-1 axis in a large cohort of ß-thalassemia major adult patients: a cross-sectional study. J Endocrinol Invest.2022; 45:1439–45. doi: 10.1007/s40618-022-01780-z.
80. Christoforidis A, Maniadaki I, Stanhope R. Growth hormone / insulin-like growth factor-1 axis during puberty. Pediatr Endocrinol Rev. 2005;3(1):5-10. PMID: 16369208.
81. Shahramian I, Noori NM, Teimouri A, Akhlaghi E, Sharafi E. The Correlation between Serum Level of Leptin and Troponin in Children with Major Beta-Thalassemia. Iran J Ped Hematol Oncol. 2015;5(1):11-7. PMID: 25914798.
82. Al-Naama LM, Hassan MK, Abdul Karim MM. Evaluation of Serum Leptin Levels and Growth in Patients with β-Thalassaemia Major. Anemia. 2016; 2016:8454286. doi: 10.1155/2016/8454286.
83. Perrone L, Perrotta S, Raimondo P, et al. Inappropriate leptin secretion in thalassemia: a potential cofactor of pubertal timing derangement. J Pediatr Endocrinol Metabo. 2003;16(6):877–81. doi: 10.1515/jpem.2003.
84. Shahramian I, Akhlaghi E, Ramezani A, et al. A study of leptin serum concentrations in patients with major Beta-thalassemia. Iran J Ped Hematol Oncol. 2013;3(2):59-63. PMID: 24575271.
85. Biswas B, Naskar NN, Basu K, et al. Malnutrition, Its Attributes, and Impact on Quality of Life: An Epidemiological Study among β-Thalassemia Major Children. Korean J Fam Med. 2021;42(1):66-72. doi: 10.4082/kjfm.19.0066.
86. Elalfy MS, Farid MN, Labib JH, RezkAllah HK. Quality of life of Egyptian b-thalassemia major children and adolescents. Egypt J Haematol 2014; 39:222-6. doi: 10.4103/1110-1067.153963
87. Hakeem GLA, Mousa SO, Moustafa AN, et al. Health-related quality of life in pediatric and adolescent patients with transfusion-dependent ß-thalassemia in upper Egypt (single center study). Health Qual Life Outcomes. 2018 ;10;16(1):59. doi: 10.1186/s12955-018-0893-z.
88. Fung EB, Kwiatkowski JL, Huang JN, et al. Zinc supplementation improves bone density in patients with thalassemia: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2013;98 (4):960–71.doi.org/10.3945/ajcn.112.049221
89. Arcasoy A, Cavdar A, Cin S,. Effects of zinc supplementation on linear growth in beta-thalassemia (a new approach). Am J Hematol. 1987;24(2):127-36. doi: 10.1002/ajh.2830240203.
90. Ghahramanlu E, Banihashem A, Mirhossini NZ, et al. Effect of zinc supplementation on serum antibody titers to heat shock protein 27 in patients with thalassemia major. Hematology. 2014;19(2):113-9. doi: 10.1179/1607845413Y.0000000099.
91. Rashidi M, Aboomardani M, Rafraf M, et al. Effects of Vitamin E and Zinc Supplementation on Antioxidants in Beta thalassemia major Patients. Iran J Pediatr. 2011;21 (1) :8-14. PMID: 23056757.
92. d'Arqom A, G Putri M, Savitri Y, et al. Vitamin and mineral supplementation for β-thalassemia during COVID-19 pandemic. Future Sci OA. 2020 ;18;6(9): FSO628. doi: 10.2144/fsoa-2020-0110.
93. Tesoriere L, D'arpa D, Butera D, et al. Oral supplements of vitamin E improve measures of oxidative stress in plasma and reduce oxidative damage to LDL and erythrocytes in beta-thalassemia intermedia patients. Free Radic. Res. 2001; 34 (5):529–40. doi: 10.1080/10715760100300461.
94. Sutipornpalangkul W, Morales NP, Unchern S, et al. Vitamin E supplement improves erythrocyte membrane fluidity of thalassemia: an ESR spin labeling study. J Med Assoc Thai. 2012;95(1):29–36. PMID: 22379738.

95. Elalfy MS, Saber MM, Adly AM, et al. Role of vitamin C as an adjuvant therapy to different iron chelators in young β-thalassemia major patients: efficacy and safety in relation to tissue iron overload. Eur J Haematol. 2016; 96(3):318–26. doi: 10.1111/ejh.12594.
96. Fung EB, Aguilar C, Micaily I, et al. Treatment of vitamin D deficiency in transfusion-dependent thalassemia. Am. J. Hematol.2011; 86(10):871–3. doi: 10.1002/ajh.22117.
97. Soliman A, Adel A, Wagdy M, et al. Calcium homeostasis in 40 adolescents with beta-thalassemia major: a case-control study of the effects of intramuscular injection of a megadose of cholecalciferol. Pediatr Endocrinol Rev. 2008;6 (Suppl 1):149-54. PMID: 19337170.
98. Soliman A, De Sanctis V, Yassin M. Vitamin D status in thalassemia major: an update. Mediterr. J Hematol Infect Dis.2013; 5(1), e2013057–e2013057. doi: 10.4084/MJHID.2013.057.
99. Thiagarajan NR, Kumar CGD, Sahoo J, et al. Effect of Vitamin D and Calcium Supplementation on Bone Mineral Content in Children with Thalassemia. Indian Pediatr. 2019;56(4):307-10. PMID: 31064900.
100. Toptas B, Baykal A, Yesilipek A, et al. L-carnitine deficiency and red blood cell mechanical impairment in beta-thalassemia major. Clin Hemorheol Microcirc. 2006;35(3):349-57. PMID: 16899956.
101. El-Beshlawy A, Youssry I, El-Saidi S, et al. Pulmonary hypertension in beta-thalassemia major and the role of L-carnitine therapy. Pediatr Hematol Oncol. 2008;25(8):734-43. doi: 10.1080/ 08880 010802244035.
102. Karimi M, Mohammadi F, Behmanesh F, et al. Effect of combination therapy of hydroxyurea with l-carnitine and magnesium chloride on hematologic parameters and cardiac function of patients with beta-thalassemia intermedia. Eur J Haematol. 2010;84(1):52-8. doi: 10.1111/j.1600-0609.2009.01356. x.
103. Shahidi M, Hashemi SR, Fattahi N, et al. The Effects of L-Carnitine on Echocardiographic Changes in Patients With β-Thalassemia Major and Intermedia. J Pediatr Hematol Oncol. 2020;42(6):386-90. doi: 10.1097/MPH.0000000000001850.
104. Egitto, Elizabeth A, Scott MAJ. Does folic acid supplementation have a role in the treatment of anemia associated with beta thalassemia? Evidence-Based Pract. 2016:19(2):14 doi: 10.1097/ 01.EBP. 0000541162.39463.
105. Mojtahedzadeh F, Kosaryan M, Mahdavi MR, et al. The effect of folic acid supplementation in beta-thalassemia major: a randomized placebo-controlled clinical trial. Arch Iran Med. 2006;9(3):266-8. PMID: 16859064.
106. Leung CF, Lao TT, Chang AM. Effect of folate supplement on pregnant women with beta-thalassaemia minor. Eur J Obstet Gynecol Reprod Biol. 1989;33(3):209-13. doi: 10.1016/0028-2243(89)90131-7.
107. Hossain A, Khatun MA, Islam M, Huque R. Enhancement of Antioxidant Quality of Green Leafy Vegetables upon Different Cooking Method. Prev Nutr Food Sci. 2017;22(3):216-22. doi: 10.3746/ pnf.2017.22.3.216.
108. Meccariello R, D'Angelo S. Impact of Polyphenolic-Food on Longevity: An Elixir of Life. An Overview. Antioxidants (Basel). 2021;10(4):507. doi: 10.3390/antiox10040507.
109. Ishikawa SI, Tamaki S, Arihara K, Itoh M. Egg yolk protein and egg yolk phosvitin inhibit calcium, magnesium, and iron absorptions in rats. J Food Sci. 2007;72(6):S412-9. doi: 10.1111/j.1750-3841.2007.00417.x.
110. Puglisi MJ, Fernandez ML. The Health Benefits of Egg Protein. Nutrients. 2022;14(14):2904. doi: 10.3390/nu14142904.
111. Cook JD, Noble NL, Morck TA, et al. Effect of fiber on non-heme iron absorption. Gastroenterology. 1983;85(6):1354-8. PMID: 6313466.
112. Piskin E, Cianciosi D, Gulec S, et al E. Iron Absorption: Factors, Limitations, and Improvement Methods. ACS Omega. 2022;7(24):20441-56. doi: 10.1021/acsomega.2c01833.
113. Disler PB, Lynch SR, Charlton RW, et al. The effect of tea on iron absorption. Gut. 1975;16(3):193-200. doi: 10.1136/gut.16.3.193.
114. Kaltwasser JP, Werner E, Schalk K, et al. Clinical trial on the effect of regular tea drinking on iron accumulation in genetic haemochromatosis. Gut. 1998;43(5):699-704. doi: 10.1136/gut.43.5.699.
115. Cross AJ, Harnly JM, Ferrucci LM, et al. Developing a heme iron database for meats according to meat type, cooking method and doneness level. Food Nutr Sci. 2012;3(7):905-13. doi: 10.4236/ fns. 2012.37120.
116. Osna NA, Donohue TM Jr, Kharbanda KK. Alcoholic Liver Disease: Pathogenesis and Current Management. Alcohol Res. 2017;38(2):147-61. PMID: 28988570.
117. Christides T, Sharp P. Sugars increase non-heme iron bioavailability in human epithelial intestinal and liver cells. PLoS One. 2013;8(12):e83031. doi: 10.1371/journal.pone.0083031.
118. Rippe JM, Sievenpiper JL, Lê KA, et al. What is the appropriate upper limit for added sugars consumption? Nutr Rev. 2017 ;75(1):18-36. doi: 10.1093/nutrit/nuw046.

Correspondence:
Received: 15 April 2023
Accepted: 15 May 2023
Ashraf Soliman, MD PhD FRCP
Professor of Pediatrics and Endocrinology
Department of Pediatrics
Hamad Medical Centre, Doha, Qatar
Po Box 3050
Phone +97455983874
E-mail : Atsoliman@yahoo.com