Management of Endocrine Complications Affecting Survival and Quality of Life in Children and Adolescents with Thalassemia Major: A Single Center Experience

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Abstract

BACKGROUND/AIMS: Although advances for treating beta-thalassemia major have improved the survival of patients, endocrine complications are still quite common in these patients. These complications continue to negatively affect the survival and quality of life of patients with thalassemia major. This study aimed to determine the frequency and distribution of endocrine complications and to investigate the relationship between these complications and serum ferritin levels in children and adolescents followed up with the diagnosis of beta-thalassemia major.

MATERIALS AND METHODS: Fifty-eight children and adolescents (female/male: 27/31, mean age 12.6±5.16 years) diagnosed with thalassemia major were included in the study. Anthropometric (body weight and height standard deviation score), laboratory and radiological evaluations according to International Network of Endocrine Complications in Thalassemia (ICET) recommendations were performed.

RESULTS: The median serum ferritin level was 2,969 ng/mL (562–10,251 ng/mL). In this study, the rate of at least one endocrine complication was 83% (n=48). Fifteen of them (31%) were under 10 years of age. The most common endocrine complications were vitamin D deficiency (53%), short stature (45%), osteopenia (34%), pubertal disorder (mean 25% for each sex) and osteoporosis. Ferritin levels did not correlate with anthropometric, laboratory parameters and endocrine complications.

CONCLUSION: Regular monitoring of growth, vitamin D status, puberty, and all other endocrine functions is important to improve the quality of life of patients with thalassemia major. Increasing the quality of life and survival of these patients may be possible with early diagnosis and treatment of endocrine complications.

Keywords: Hemoglobinopathy, thalassemia major, endocrinopathies, children and adolescents

INTRODUCTION

Beta-thalassemia major (BTM) is a hereditary disease caused by a defect in hemoglobin synthesis. The basis of BTM therapy is transfusion. The main purpose of transfusion therapy is to keep the hb levels between 9 and 10 g/dL before transfusion. For this purpose, blood transfusion is applied at 2–4 weeks intervals. Iron chelation treatments are used to prevent iron buildup and related complications. Splenectomy is performed in patients with transfusion requirement >200 to 220 mL RBC/kg per year and developing symptoms of hypersplenism. In patients with
adolescents are few. Most of the previously reported studies were performed on bone mineral density (BMD) in patients older than 10 years old. Group and dual-energy X-ray absorptiometry for evaluation of bone age (X-ray of wrist and hand), serum sex steroids (testosterone/estradiol), luteinizing hormone (LH), follicle stimulating hormone (FSH), glucose (IFG), serum insulin-like growth factor (IGF)-I (only in patients with short stature), parathyroid hormone (PTH), fasting glucose/insulin and oral glucose tolerance testing (OGTT) in case of impaired fasting glucose (IFG), serum insulin-like growth factor (IGF)-1 (only in patients with short stature), bone age (X-ray of wrist and hand), luteinizing hormone (LH), follicle stimulating hormone (FSH), and sex steroids (testosterone/estradiol) in the pubertal age group and dual-energy X-ray absorptiometry for evaluation of bone mineral density (BMD) in patients older than 10 years old.6

The recommended parameters for annually Endocrine screenings in pediatric and adult patients with BTM according to International Network of Clinicians for Endocrinopathies Complications in Thalassemia (ICET) guidelines are serum thyroid stimulating hormone (TSH) and free T4, serum calcium, phosphate, magnesium, alkaline phosphatase, vitamin D, and parathyroid hormone (PTH), fasting glucose/insulin and oral glucose tolerance testing (OGTT) in case of impaired fasting glucose (IFG), serum insulin-like growth factor (IGF)-1 (only in patients with short stature), bone age (X-ray of wrist and hand), luteinizing hormone (LH), follicle stimulating hormone (FSH), and sex steroids (testosterone/estradiol) in the pubertal age group and dual-energy X-ray absorptiometry for evaluation of bone mineral density (BMD) in patients older than 10 years old.6

Most of the previously reported studies were performed on adolescents and adults, studies involving only children and adolescents are few.6,7,9 Therefore, we aimed to determine the frequency of endocrine complications and to evaluate the factors affecting these complications in children and adolescents diagnosed with BTM.

**MATERIALS AND METHODS**

A total of 58 children and adolescents followed up with the diagnosis of BTM in pediatric endocrinology and pediatric hematology outpatient clinics were included in the study [female (F)/male (M): 27/31]. BTM was diagnosed by genetically in 31 patients and by transfusion dependence and hemoglobin electrophoresis in others. Transfusions were administered monthly during infancy and subsequently at intervals of 2–4 weeks. The pretransfusion Hb level of the patients was 9–10 g/dL.

Patients were followed up every 6 months for growth and endocrine complications according to ICET (International Network of Clinicians for Endocrinopathies Complications in Thalassemia) recommendations in the endocrine outpatient clinic and data were recorded.8 Physical was examined by the same physician (S.T.). Weight was measured using a calibrated digital scale and length measurements were made using a stadiometer fixed to the wall. The body mass index was calculated by dividing the body weight (kg) by the square of the meter of height (m²).

Estimation of the child’s genetic height potential (target height) is an important tool in evaluating growth disorders. Midparental height (MPH) is used for this purpose. It represents the child’s expected height based on parental heights. Midparental height, was calculated for boys as [(father height + (mother height + 13 cm))/2, for girls as [mother height + (father height-13 cm)]/2.

Anthropometric standard deviation scores (SDS) were evaluated according to age and sex-matched norms for Turkish children.10 Height below -2 SDS was defined as short stature. The growth velocity of the patients were calculated according to height difference at least 6-month via data in the files. According to this, growth velocity below -2 SDS was considered insufficient growth velocity.11

Pubertal status was evaluated according to Tanner criteria.12 Absence of breast development until 13 years of age in girls and the absence of testicular growth (>4 mL) until 14 years of age in boys was defined as pubertal delayed.

Patients with thalassemia intermedia were excluded from the study. Written consent was obtained from the guardians of all patients.

In the follow-up of the patients, the following tests were performed according to ICET recommendations; serum TSH and free T4 (FT4), calcium, phosphate, magnesium, alkaline phosphatase (ALP), 25OH vitamin D and PTH, fasting glucose/insulin. An oral glucose tolerance test (OGTT) was performed.
in case of IFG. Serum insulin-like growth factor 1 (IGF-1) and bone age (hand and wrist radiograph) were analysed in patients with only short stature. In patients with the pubertal age group were performed luteinizing hormone (LH), FSH and sex steroids (testosterone/estradiol). Follicle-stimulating hormone and luteinizing hormone values were measured by immuno-chemiluminescence (ICMA) method. Bone mineral density (BMD) was assessed with dual X-ray absorptiometry (DXA) in patients older than 10 age years. Growth hormone (GH) stimulation tests were performed on eight patients. These patients had short stature, IGF-1 levels were <-2 SDS according to reference values appropriate age and sex and growth velocity were low.\textsuperscript{11,13} Clonidine [0.15 mg/m² peroral (PO)] and glucagon (<15 kg, ½ ampoule, >15 kg, 1 ampoule, intramuscular) were used for GH stimulation tests. For both stimulation tests for peak GH level <10 ng/dL was considered growth hormone deficiency.

FSH, LH, estradiol and/or total testosterone levels were evaluated in 15 girls and 13 male patients whose chronological age was ≥13 and ≥14 years, respectively. Gonadotropin releasin hormone (GnRH) Ferring Pharmaceuticals (LHRH) stimulation test was performed to evaluate hypothalmo-pituitary axis in three girls and four boys whose had pubertal delay. Blood samples were taken at baseline and 20, 40 and 60 min after intravenous injection of gonadorelin acetate to assess LH, FSH, estradiol/testosterone levels.

25-OH-vitamin D level 15–19 ng/mL was defined as vitamin D insufficiency and 25-OH-vitamin D level <15 ng/mL was defined as vitamin D deficiency. For vitamin D insufficiency, daily 1,000 IU vitamin D PO was administered for 6–8 weeks, while all patients with vitamin D deficiency received a single dose of 150–300 thousand units of Stoss Vitamin D replacement treatment.\textsuperscript{14}

Low dose (1 mcg tetracosactid (Synacthen; Novartis) Adrenocorticotropin (ACTH) stimulation test was performed in 8 patients whose serum cortisol level measured at least 2 times in the early morning was <10 mg/dL. Cortisol level was measured at baseline and at the 30\textsuperscript{th} and 60\textsuperscript{th} minutes after tetracosactid intravenous injection.

An oral glucose tolerance test was performed on six patients had IFG [with a dose of 1.75 g/kg (maximum 75 g glucose)]. Serum glucose and insulin levels were measured at baseline and 60 and 120 min after oral glucose administration. IGT was defined as glucose level >140 mg/dL but also <200 mg/dL. Diabetes mellitus (DM) was diagnosed on the basis of a glucose level >200 mg/dL or a history of insulin therapy.\textsuperscript{15} Biochemical analysis were performed using Abbott Architect C16000 and Roche cobas e601 Autoanlyser.

Bone age was determined by nondominant wrist radiograph evaluated according to Greulich and Pyle method using the same physician (S.T.). Bone mineral density (BMD) of 30 patients older than 10 age years was evaluated with dual X-ray absorptiometry (DXA) method. Z-scores of BMD of all body except the head were adjusted for bone age and sex were recorded. Z scores >-1, -1 to -2 and <-2 and clinically significant fracture history (lower extremity long bone fracture, vertebral compression fracture, or two or more long bone fractures in the upper extremity) were accepted as normal, osteopenic and osteoporotic, respectively.\textsuperscript{16}

The mean ferritin level of the last one year was calculated.

This study was approved by the Ethics Committee of University of Health Sciences Turkey, Diyarbakir Gazi Yaşargil Training and Research Hospital (decision number: 241).

### Statistical Analysis

SPSS 20.0 software was used for all statistical analysis. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine normal distribution. Variables showing a normal distribution were given as mean ± standard deviation, and variables without normal distribution were given as median (range). Descriptive statistics were made. Mean and standard deviation values of continuous and categorical variables were calculated. Independent sample t-test was used for continuous variables Univariate correlation analysis and Pearson correlation analysis were performed for the relationship between parameters. P-value <0.05 was considered statistically significant.

### RESULTS

The mean height Z Score was -1.52±1.42, the mean weight z score was -1.27±1.44 and the mean body mass index (BMI) Z score was -0.55±1.10. There was no statistically significant difference between the mean height Z score (-1.52±1.42), and the midparental height Z score (-0.98±0.84) in the study group (p=0.03). Endocrine complications in patients with beta thalassemia major are summarized in Table 1. 45% of the patients (n=26, F/M: 9/17) had short stature. Serum IGF-1 levels were <-2 SDS (-1.96±1.21) (30.6–441ng/mL) (according to reference values

| Table 1. Endocrine complications of the patients |
|-----------------------------------------------|
| Complication                  | n (%)              |
| Short stature/GH deficiency     | 26/5 (45/19%)      |
| Vitamin D deficiency/insufficiency | 14/31 (24/53%)    |
| Osteopenia/osteoporosis        | 20/8 (34/14%)      |
| Hypogonadism (F/M)             | 2/2 (3.5/3.5%)     |
| Pubertal delay (F/M)           | 1/2 (2/3.5%)       |
| Overt/subclinic hypothyroidism | 2/3 (3.5/5%)       |
| Hypoparathyroidism             | 2 (3.5%)           |
| Impaired fasting glucose       | 6 (11%)            |
| Impaired glucose tolerance     | 3 (5%)             |
| Adrenal insufficiency          | 3 (5%)             |

GH: growth hormon, F/M: female/male, n: number.
of Turkish children adjusted age and sex) in 92% of patients with short stature. In eight patients with short stature because of inadequate growth velocity were performed two GH stimulation test. There was no hypothyroidism or any other endocrine dysfunction in all short stature cases with or without growth hormone deficiency. Pubertal status was evaluated in 15 girls aged ≥13 years. Three of 15 patients (20%) had low serum basal LH levels (LH <0.3 IU/mL) and Tanner stage 1 breast development. Gonadorelin acetate stimulation test (GnRH) was applied to these patients. Two patients had peak LH <5 IU/L and 17-beta-estradiol replacement was started with the diagnosis of possible hypogonadotropic hypogonadism. One patient with peak LH ≥5 IU/mL was accepted as delayed puberty.

The mean serum vitamin D level was 13.04±6.07 ng/mL. Vitamin D insufficiency was detected in 31 patients (53%) and vitamin D deficiency was detected in 14 patients (24%). For vitamin D insufficiency, daily 1,000 IU PO (6–8 weeks) vitamin D replacement was administered. All patients with vitamin D deficiency received 150–300 thousand units of single dose vitamin D PO (Stoss treatment). While vitamin D levels of all patients who received stop therapy reached normal levels, vitamin D deficiency continued in 18.6% of the patient who received daily 1,000 IU PO vitamin D.

The mean BMD Z score adjusted for age and sex was -2.08±1.64. While 34% (13 girls, seven boys) of the patients were osteopenic, 14% (five girls, three boys) were osteoporotic. There was a negative correlation between BMD (in gr/cm²) and 25-OH-D level (r=-0.56, p=0.01). Hypoparathyroidism was detected in two girls aged 16 and 17 years (3.4%). Hypocalcemia was not detected in the first decade of life of these patients. Calcium was 4.8 and 5.9 mg/dL, while phosphorus was 7.2 and 7.1 mg/dL and PTH was 7 and 8 pg/mL, respectively. Vitamin D levels were normal in these patients.

Two patients had overt hypothyroidism and three had subclinical hypothyroidism (normal free T4 level and increased TSH level). Anti-thyroid peroxidase antibody and anti-thyroglobulin antibody were negative in these patients. They had thyroid ultrasonography that was normal morphology and echogenicity.

The mean level of serum basal cortisol was 10.33±3.85 mg/dL. On eight patients whose had at least two basal cortisol levels <10 mg/dL early in the morning were performed a low dose (1 mcg) ACTH stimulation test. Adrenal insufficiency was detected in three of eight patients (5.1%) when a minimum peak cortisol level was used 18 mg/dL, according to ACTH stimulation test. The mean age of these patients was 14.9±3.1 years. These patients were completely asymptomatic for adrenal insufficiency.

OGTT was performed on six patients with IFG. IGT was diagnosed in three of these patients (5.1%). In this study was not determined overt DM.

The pretransfusion Hb level of the patients was 9–10 g/dL. The final mean ferritin level was 3,086±2,046 ng/mL, and the median ferritin level was 2,969 ng/mL (562–10,251). The mean transfusion year was 9.58±5.01 years. The age of initiation of iron chelation treatment was 2.21±0.3 years. The anthropometric and biochemical data of the patients are summarized in Table 2. There was no correlation between ferritin level and onset age of chelation treatment, transfusion year, anthropometric and biochemical parameters (glucose, calcium, ALP, PTH, 25-OH-D, free T4, TSH, LH, FSH, testosterone, estradiol, cortisol, IGF-1).

Thirty patients were genetically diagnosed (52%). Of these patients 19 had IVS I-110 homozygous mutation, one had IVS I-110 heterozygous mutation, three had codon del AA homozygous mutation, four had IVS I-6 IVS I-110 double heterozygous mutation, two had IVS I-110 codon eight del double heterozygous mutations and one had codon 44 heterozygous delta-beta deletions. Genetic studies was not conducted in other patients. There was no significant difference in terms of endocrine complications between patients with and without genetic diagnosis (p=0.35).

**DISCUSSION**

Recently, the development of treatment options in patients with beta thalassemia has increased the survival rates. Therefore, the importance of diagnosis and treatment of endocrine complications has also increased to have a higher quality of life.

In patients with BTM, the incidence of complications increases with age (4–6). In our study, the mean age of endocrine complications was 12.6±5.16 years.

Blood transfusion can lead to iron overload resulting in a high incidence of endocrine abnormalities in children and adolescents. Excessive iron is deposited in most tissues and
endocrine organs are also frequently affected organs. It has already been reported that the iron overload is the major cause of endocrinopathies in thalassemia.17

The most common reported endocrine complications in patients with talassemia major are growth retardation, vitamin D insufficiency/deficiency and puberty problems.6,8 In our study, the most common endocrine complications were vitamin D deficiency, growth retardation, osteopenia and pubertal delay-gonadal insufficiency, respectively. When growth retardation was included, 82% of the patients had at least one endocrine complication. All the patients whose have endocrine complications except growth retardation and osteoporosis/osteopenia were over 12 years of age.

The pathogenesis of growth retardation, which is a common complication in BTM, is heterogeneous. Chronic anemia, iron overload, malnutrition despite increased caloric requirement, chronic liver and renal insufficiency, hypothyroidism due to the accumulation of iron in various endocrine organs, delayed puberty/hypogonadism and GH deficiency are the main factors contributing to growth retardation.9,10 In previous studies, the prevalence of growth retardation was reported to be 25%–69% and the prevalence of GH deficiency was reported to be between 8% and 54%.5–7,9,10 In our study, growth retardation was determined to be 45% and growth hormone deficiency was determined in 8.5%. These results were similar to the literature.

Pubertal delay/hypogonadism is a common endocrine complication that affect growth in BTM. In the previously published studies, delayed puberty/hypogonadism was reported in 12.2%–38% of women, 22.9%–67% of men and 41.6%–80% of pediatric patients.10–21 In our study, delayed puberty-hypogonadism was detected in 3 (20%) of 15 female patients and four (30%) of 13 male patients. In a study, Low et al.22 reported that only 32% of 41 BTM patients whose had completed the age of 14 years entered puberty spontaneously. In another study, Bronspiegel-Weintrob et al.23 reported that entered puberty in time in the 90% of the patients that chelation therapy was started before 10 years of age. In addition, only 38% of the patients whose started chelation treatment late were entered puberty spontaneously.

The prevalence of vitamin D deficiency and insufficiency is also high in the general population. In Turkey, although it may change with age, gender, and the seasons prevalence of vitamin D deficiency/insufficiency in children and adolescents was reported to be 8%–61%.24 Even so the prevalence of vitamin D deficiency/insufficiency in children with BTM is expected to be higher compared to the general population due to insufficient hydroxylation in the liver and to chelation therapy, which increases excretion of vitamin D.4 In this study the prevalence of vitamin D deficiency and insufficiency together was calculated as approximately 77.5%. This rate is higher than general population. The prevalence of vitamin D deficiency and insufficiency are ranged from 12% to 37% and 47.8% to 69.8% respectively, in the literature.25,26 The prevalence of vitamin D deficiency and insufficiency that the most common complication in our study, was 24% (n=14) and 53% (n=31), respectively. Our results were similar to previous reports.

Pediatric and adolescent BTM population have already experienced compliance problems to transfusion/chelation therapy.5–7 In this population probably is expected also the lack of compliance to long-term Vitamin D PO therapy. While vitamin D levels arrived normal levels in all patients receiving stop therapy, vitamin D insufficiency continued in 18.6% of patients administering long-term oral vitamin D. Therefore, stts treatment of vitamin D should be preferred for treatment of vitamin D deficiency/insufficiency due to lack of compliance long-term Vitamin D PO therapy in these patients.

There was no co-relation between vitamin D and ferritin levels in our study, similar to the previous reports.5,25,26

Osteoporosis is a common problem in BTM. Increased iron load, cortical thinning due to bone marrow expansion, adverse effects of chelating agents on calcium and phosphorous absorption, hypogonadism, hypoparathyroidism and decreased IGF-1

Table 2. Anthropometric and laboratory data of the patients

| Mean ± SDS |
| Age (decimal years) | 12.6±5.16 |
| Gender (F/M) | 27/31 |
| Weight Z score | -1.27±1.44 |
| Height Z score | -1.52±1.42 |
| BMI Z score | -0.55±1.10 |
| Serum Ferritin (ng/mL) | 3,086±2,046 |
| Calcium (mg/dL) | 3,086±2,046 |
| 25 OH Vitamin D (ng/mL) | 13.04±6.07 |
| PTH (pg/mL) | 49.4±36.62 |
| ACTH | 27.25±15.37 |
| Cortisol (mg/dL) | 10.33±3.85 |
| fT4 (ng/dL) | 1.18±0.28 |
| TSH (IU/mL) | 2.77±0.91 |
| Pretransfusion Hb (g/dL) | 8.2±0.9 |
| Chelation starting age (decimal years) | 2.21±0.3 |
| Years of transfusion | 9.50±5.01 |
| DXA Z score | -2.08±1.64 |
| IGF-1 Z score | -1.96±1.21 |

F/M: female/male, BMI: body mass index, DXA: dual X-ray absorptiometry, PTH: parathyroid hormone, ACTH: Adrenocorticotropin, fT4: free T4, TSH: thyroid stimulating hormone, Hb: hemoglobin, IGF-1: insulin like growth factor, SDS: standard deviation scores, n: number.
level (positive effect on IGF-1 osteoblasts) increase the risk of osteoporosis in these patients.  
Bone pain and bone fracture owing to osteoporosis are important factors affecting the morbidity of these patients. In the literature, the prevalence of osteoporosis and osteopenia in BTM has been reported to be between 22.2% and 50.7%. In our study, 20 patients (34%) were osteopenic (13 girls, seven boys) and eight patients (13.6%) were osteoporotic (five girls, three boys).

Hypothyroidism is a complication mostly seen after the second decade. Primary hypothyroidism due to iron accumulation in the thyroid gland is more common in BTM. In previous studies were reported that the prevalence of overt hypothyroidism and subclinical hypothyroidism ranged from 4.2% to 18.8% and 2.12% to 22.8%, respectively. In our study, primary hypothyroidism was detected in two patients (3.4%) and subclinical hypothyroidism was found in three patients (5.1%). All of our patients were older than 12 years. In our study hypothyroidism prevalence was lower than the literature. This condition can be explained by the lower mean age of our study population.

In hypoparathyroidism that a rare complication in BTM patients, parathyroid hormone release is suppressed and bone resorption is increase because of iron accumulation in the parathyroid gland. The prevalence of this complication that affecting both sexes equally is reported as 3.6% to 22.5%. Overt hypoparathyroidism was detected in 2 patients in our study. The mean age of overt hypoparathyroidism is reported 16.9 to 19 years in the literature. Our patients were 16 and 17 years old. In a study from our country included of 45 patients with thalassemia major hypoparathyroidism was not reported. However, subclinical hypoparathyroidism (PTH levels are decreased, calcium and phosphate are normal) are more common than in overt hypoparathyroidism in patients with BTM. Subclinical hypoparathyroidism was not detected in our study.

Adrenal insufficiency is a rare but life-threatening complication in patients with BTM and is usually detected at older ages. Adrenal insufficiency prevalence has been reported to be between 15.5% and 61% in different studies. Adrenal insufficiency prevalence was detected 5.1% in our study. In our study the mean age of patients had adrenal insufficiency was 14.9±3 years. The heterogeneity of the tests used for diagnosis and of the average age of the study populations can explain the wide prevalence range in the literature and the low prevalence rate in our study. The mean age of our study population was 12.6±5.16 years.

For the diagnosis of adrenal insufficiency in patients with BTM, it is necessary to evaluate cortisol levels at least once a year. Kortisol level below 10 mgr/dL suggest suspicious adrenal insufficiency, while cortisol level below 3 mgr/dL support the diagnosis of adrenal insufficiency. Low-dose ACTH stimulation test was performed only for patients whose had early morning low cortisol levels (eight patients) in our study. We detected adrenal insufficiency in three of eight patients (5.1%). All of these patients were asymptomatic for adrenal insufficiency. We planned to give glucocorticoid treatment before stressful events, surgeries and severe diseases to these patients.

Impaired glucose tolerance (IGT) and DM are well-known complications in BTM patients. These complications were reported in older ages and less frequently. In these cases initially are increased insulin resistance rather than decreased insulin secretion. Decreased insulin secretion appears in the later period as a late finding of iron accumulation in the pancreas. In previous studies, the prevalence of IGT and DM was reported to be between 2%–13%, 4% to 19.4%, respectively. In our study, three patients were diagnosed with impaired glucose tolerance (IGT) (5.1%) but was not detected overt DM. Hepatitis C virus infection, starting chelation therapy in advanced age, high ferritin level, advanced age, frequency of transfusion, family history of diabetes and high liver iron concentration have been reported as the main causal factors for DM in these patients. Over 10 years old children with BTM should be monitored regularly for IFFG, IGT and overt DM.

Proper chelation of iron overload could improve the quality of life of these patients and decrease the endocrine and cardiac complications. In our patients, deferasirox was used as iron chelator. Chelation was started when the ferritin levels exceeded 1,000 ng/mL and the patient was 2 years old. Most patients were on a regular transfusion regimen and were using regular chelator. The most important factors affecting serum ferritin levels are regular use of chelation therapy, infections, age and geographic differences. In a study by Bandyopadhyay et al. was shown that mean serum ferritin was 1,750 ng/mL in 1–5 years age group, and this increased to 3,650 ng/mL in 11–15 years older patients. Cunningham et al. reported that mean serum ferritin level of beta thalassemia patients, in North America to be 1,696 ng/mL. In our study, mean serum ferritin level was 3,086±2,046 ng/mL. However, Choudhry et al. reported mean serum ferritin levels to be 6,723 ng/mL in India. Although iron overload is considered leading cause of endocrinopathies in BTM patients, are not showed significant relation between serum ferritin and endocrinopathies in most of the studies in literature. In our study in accordance with the literature, we were not determined any correlation between endocrine complications and level of ferritin and the starting age to chelation therapy. Therefore, it is not correct to predict and evaluate endocrine complications based on ferritin level. Although serum ferritin is quantitative, non-invasive method for measuring body iron, it is not an optimal indicator of iron status and may be insufficient to show tissue iron accumulation in patients with BTM. More precise methods such as T2*MRI and liver iron concentration (LIC) may be used instead ferritin. However, it is a fact that it should not be
CONCLUSION

As a result, in this study although the major advances in treatment increase the life expectancy of patients with BTM, endocrine problems continue to adversely affect the quality of life of these patients. Monitoring of patients with BTM in terms of endocrine complications, regardless of ferritin level, is essential to improve the quality of life of these patients.

MAIN POINTS

- Despite advances for treating major thalassemia, endocrine complications seen in these patients are still common.
- These data provide information about the frequency and distribution of endocrine complications in children and adolescents with thalassemia major.
- These data provide information about the approach to endocrine complications.
- The quality of life of these patients increases significantly with the early diagnosis and appropriate treatment of endocrine complications.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Turkey, Diyarbakır Gazi Yaşargil Training and Research Hospital (decision number: 241).

Informed Consent: Written consent was obtained from the guardians of all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.T., H.S., Design: S.T., H.S., Data Collection and/or Processing: S.T., H.S., Analysis and/or Interpretation: S.T., H.S., Literature Search: S.T., H.S., Writing: S.T., H.S., Critical Review: S.T., H.S.

DISCLOSURES

Conflict of Interest: The authors declare no conflict of interest.

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