ENDOCRINOLOGY RESEARCH AND PRACTICE

SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TURKEY

Endocrine Disorders in Adult Beta-Thalassemia Patients: Insights from a Long-Term Follow-Up

ORIGINAL ARTICLE
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ABSTRACT

Objective: There are limited studies regarding endocrine complications in Turkish adult thalassemic patients. Data regarding newly emerging endocrine complications in the long-term monitoring of adult patients with beta-thalassemia are also quite limited.

Methods: The study was a single-center cohort study involving 103 adult patients with beta-thalassemia.

Results: The most frequent endocrine disorder was vitamin D insufficiency (69%), whereas the most common endocrine complications were hypogonadism (56%) and osteoporosis (37%) in thalassemic patients. Three or more endocrine disorders were present in 42% of the patients. Patients with hypogonadism had higher ferritin levels ($P=.014$), lower hemoglobin concentrations ($P=.028$), and increased myocardial iron deposition ($P=.002$) compared to those without hypogonadism. There was also a link between 5-year calculated mean ferritin levels and fasting plasma glucose ($r=0.29$, $P=.004$) and 75 g oral glucose tolerance test second-hour glucose levels ($r=0.46$, $P=.001$). Osteoporosis was more common in patients with hypogonadism (51% vs. 21%, $P=.003$) and diabetes (75% vs. 35%, $P=.027$). The remaining endocrine problems, on the other hand, were not linked to thalassemia-related characteristics or each other. In 3 and 5 years of follow-up, 16% and 12% of patients developed a new endocrine–metabolic complication, respectively, with osteoporosis and prediabetes/diabetes being the most common.

Conclusion: A significant proportion of adult thalassemic patients have multiple endocrine–metabolic complications. All patients with thalassemia major, regardless of their ferritin levels, should be evaluated for the occurrence of endocrine complications. Endocrinologists should be especially vigilant during long-term follow-up for the development of glucose metabolism disorders and osteoporosis in adult thalassemic patients.

Keywords: Beta-thalassemia, adult, vitamin D, prediabetes, diabetes mellitus, osteoporosis, hypogonadism

Introduction

Thalassemia is one of the most frequent monogenic disorders in the world, and Turkey is among the countries where premarital screening is mandatory.[1] Iron accumulation in the liver and myocardium is the foremost contributor to morbidity and mortality in patients with beta-thalassemia.[2] Introducing more effective iron chelation treatments and supportive therapies has gradually improved patients' life expectancy. Consequently, mortality rates in this population decreased throughout the years,[3] a trend also observed in Turkey.[4]

However, with increasing age, there is a notable rise in endocrinological complications among thalassemic patients.[5] Vigilant and regular endocrinological follow-up of adult patients with beta-thalassemia becomes of utmost significance. Few studies have focused on endocrine–metabolic disorders in Turkish adult patients with beta-thalassemia, often with limited sample sizes.[6,7] The primary objectives of these studies were to investigate the relationship between pituitary iron accumulation and endocrine complications (n = 48) or to explore the connection between pancreatic iron accumulation and diabetes mellitus ($n=40$). Neither found a significant finding in the areas they investigated. Instead, the first study found a connection between cardiac iron accumulation and hypogonadism. In contrast, the second study identified a relationship between cardiac iron accumulation, serum ferritin, and fasting plasma glucose (FPG) levels. Nevertheless, a comparable prevalence of at least one endocrine complication in patients with beta-thalassemia was observed (62% and 65%, respectively). Osteoporosis and hypogonadism were the two most common endocrine complications in both studies.

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Our study aims to address the prevalent endocrine–metabolic disorders in a larger cohort of adult patients with beta-thalassemia. Additionally, we seek to explore the potential relationships between these disorders and thalassemia-related parameters routinely checked during the follow-up of these patients, such as serum ferritin levels and MRI T2-star measurements indicating iron deposition in the liver and myocardium. Newly emerging endocrine findings during long-term follow-up and their potential interactions with thalassemia-related parameters were also investigated.

Materials and Methods

Patients and Study Design

The study was designed as a single-center cohort study. Of the 2 clinically significant forms of beta-thalassemia, 93 patients with beta-thalassemia major and 10 patients with beta-thalassemia intermedia who applied to the endocrinology outpatient clinic of Hacettepe University Hospital between July 2014 and January 2022 were enrolled in the study. Absent (beta-thalassemia major) or reduced (beta-thalassemia intermedia) synthesis of the hemoglobin subunit beta (beta globin chain) was demonstrated in all patients.

Data regarding beta thalassemia, such as iron chelation therapy, splenectomy history, and parental consanguinity, were collected. The serum ferritin value at the last clinic visit was recorded (Access® Immunoassay Systems are used in our institution with an analytical sensitivity of ferritin measurement of 0.2 ng/mL). The mean ferritin values of the last 3 or 5 years (whichever is available) were computed and referred to in the text as "computed mean ferritin." Myocardial and liver T2-star values obtained from magnetic resonance imaging (MRI) studies were noted. The age and reason for the first endocrinology consultation were documented according to patient files and/or patients' statements. Data regarding any endocrine–metabolic disorder diagnosed before the current application, current or prior use of hormonal replacement therapies, antidiabetic or antiosteoporotic medications, past pathological fractures, and pubertal history were recorded according to anamnesis and patient files. The patients' height and weight, blood pressure, thyroid palpation findings, and Tanner stages[8,9] were all recorded during the physical examination. Blood samples were collected in the early morning (08:30-09:00 AM) after 8 hours of fasting for the measurements of the following: fasting plasma glucose (FPG), thyroid stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone in males, estradiol in females, adrenocorticotrophic hormone (ACTH), cortisol, growth hormone (GH), insulin-like growth factor 1 (IGF-1), creatinine, calcium (Ca^{++}), phosphorus (P), alkaline phosphatase (ALP), parathyroid hormone (PTH), and 25-hydroxy-vitamin D (25OHD). Corrected Ca (mg/dL) was calculated as "serum total Ca (mg/dL) + 0.8 [4.0 − Serum albumin (g/dL)]". Low IGF-1 levels were defined as at or below the third percentile for the given age and gender. A 250 µg intravenous tetracosactide stimulation test was used to identify patients with hypocortisolemia, defined as plasma cortisol levels less than 18 µg/dL after 30 or 60 minutes of injection.[10] Patients who had not had a 75 g oral glucose tolerance test (75 g OGTT) within the previous year were advised to have one.[11] Patients who had not had a dual-energy x-ray absorptiometry (DEXA, Lunar Prodigy Pro; GE Healthcare, Madison, Wis, USA) scan and x-ray of the thoracolumbar vertebrae in the last year were referred to these exams. Bone mineral density (BMD) measurements and T- and Z-scores of the lumbar vertebrae (L1-4) and femur (total and femur neck) were recorded.[12]

Overt and subclinical hypothyroidism, hypogonadism, hypocortisolism, primary hypoparathyroidism, prediabetes, and diabetes mellitus were all diagnosed according to the relevant guidelines.[10,11,13-15] Vitamin D deficiency was defined as 25OHD levels less than 20 µg/L.[16] Osteoporosis was diagnosed if the T- or Z-score at the spine, femur neck, or total hip was ≤−2.5 and/or if the patient had pathological fractures. Osteopenia was defined as a T- or Z-score between −1.0 and −2.5 at the spine, femur neck, or total hip.[12] Short stature was defined as height measurements at or below the third percentile for a given age and sex.

All patients were advised to attend regular endocrinology outpatient clinic visits, and follow-up data regarding new-onset hormonal disorders was collected when available.

Statistical Analysis

According to the parametric distribution assumptions, continuous variables were given as mean ± standard deviation (SD) or median (minimum–maximum). Categorical variables were given as numbers with percentages (n, %). For dichotomous variables, Fisher's exact test and the chi-square test were used to compare groups, while the Mann–Whitney *U*-test and *t*-test were used to compare continuous data, as appropriate. The Pearson and Spearman correlation analyses were used for normally and non-normally distributed variables. A multivariate logistic regression test was performed to identify possible independent risk factors for developing endocrine complications. The Statistical Package for the Social Sciences Statistics software, version 24.0, was employed for all analyses (IBM Inc., Armonk,

MAIN POINTS

- Survival rates in beta-thalassemia improved with the introduction of effective iron chelators and supportive therapies. However, with increasing age, there is a notable rise in endocrinological complications among thalassemic patients.
- This study included 103 adult patients with beta-thalassemia. The most common endocrine disorders were vitamin D deficiency, hypogonadism, and osteoporosis/osteopenia, followed by primary hypoparathyroidism. When vitamin D deficiency was excluded, the rate of three or more endocrine–metabolic complications was 40.7%.
- Patients with hypogonadism exhibited higher ferritin levels, lower hemoglobin concentrations, and increased myocardial iron deposition. Additionally, there was a positive correlation between 5-year calculated mean ferritin levels and fasting plasma glucose and 75 g oral glucose tolerance test second-hour glucose levels.
- Patients with hypogonadism and diabetes had higher rates of osteoporosis. Hypogonadism was also associated with pathological fractures.
- Osteoporosis and prediabetes/diabetes were the most common conditions that newly emerged during long-term follow-up.

NY, USA). Statistical significance was defined as a *P*-value of less than .05.

Ethics Committee Approval

The Ethics Board of Hacettepe University Faculty of Medicine approved the study with the project code GO 20/874. Informed consent has been obtained from all participants.

Results

The main characteristics of the patients are presented in Table 1. The mean age at the first endocrinology visit was 24.7 ± 0.9 years, ranging between 7 and 47 years, respectively. Figure 1 depicts the frequency (%) of endocrine–metabolic disorders in the entire study population and in patients with thalassemia major that were either diagnosed before the current application or were discovered during the evaluations. The most common endocrine disorders were vitamin D deficiency, hypogonadism, and osteoporosis/osteopenia, followed by primary hypoparathyroidism. A total of 86 patients (83.5%) of the study population had more than one endocrine–metabolic disorder at the time of study enrollment, with 63 (61%) having 3 or more. When vitamin D deficiency was excluded, the rate of 3 or more endocrine–metabolic complications was 40.7% (n = 42).

Vitamin D Deficiency

The most common endocrine disorder among patients with beta-thalassemia was vitamin D deficiency (69% in the entire cohort) (Figure 1). The prevalence of vitamin D deficiency was slightly higher than the general adult population in Turkey, which was reported to be 63.5% (95% CI: 58.8-67.9).[17] Patients with and without vitamin D deficiency had mean 25OHD levels of 11.3 ± 4.3 and 32.1 ± 9.8 µg/L, respectively. Vitamin D deficiency was unrelated to other endocrine disorders, including osteopenia/osteoporosis or fragility fractures.

Hypogonadism

Hypogonadism was the most common endocrine complication among patients with beta-thalassemia, and symptoms and/or signs related to hypogonadism were the second most common reason for patients to apply to endocrinology (Figure 1 and Table 1).

The median age at puberty in female and male patients was similar: 15 (11-27) and 16 (12-26) years, respectively (*P* = .52). Fifty-eight patients (56.3%) were diagnosed with hypogonadism before study enrollment or during the evaluations. Only patients with thalassemia major had hypogonadism, and it was all secondary. Male and female patients with thalassemia major had comparable rates of hypogonadism (54.9% vs. 57.7%, *P* = .84), with similar median ages at diagnosis [20 years (between 14 and 34 years) vs. 18 years (between 15 and 34 years), *P* = .49]. Combined oral contraceptives were the first-line treatment in females with hypogonadism, whereas intramuscular depot testosterone was in males.

The comparisons of patients with and without hypogonadism are shown in Table 2. The patients with hypogonadism had lower hemoglobin concentrations (*P* = .028), higher serum ferritin levels (*P* = .014), and lower T2-star values on myocardial MRI (*P* = .002), which indicates increased myocardial iron deposition. Hypogonadism was not associated with the other endocrine disorders except for low hip BMD measurements (*P* = .002). In multivariate analysis, none of these factors were identified as independent risk factors for developing hypogonadism.

Osteoporosis and Osteopenia

The frequency of osteoporosis and osteopenia in patients with beta-thalassemia is represented in Figure 2. Figure 3 shows the sites of

Table 1. Patient Characteristics

	All Group (n = 103)	Thalassemia Major (n = 93)	Thalassemia Intermedia (n = 10)
Age at enrollment (years ± SD)	30.4 ± 6.7	30.1 ± 6.8	32.7 ± 5.1
Gender			
Female, n (%)	52 (50.5%)	45 (48.4%)	6 (60.0%)
Male, n (%)	51 (49.5%)	48 (51.6%)	4 (40.0%)
Age at thalassemia diagnosis (years), median (minimum–maximum)	1 (0-13)	0.8 (0-13)	3 (0-7)
Parental consanguinity, n (%)	37 (43.5%)	30 (39.5%)	7 (77.8%)
Splenectomy, n (%)	73 (73.0%)	67 (74.4%)	6 (60.0%)
Iron chelation therapy, n (%)	96 (93.2%)	92 (98.9%)	4 (40.0%)
Monthly RBC transfusions (yes, %)	96 (93.2%)	92 (98.9%)	4 (40.0%)
Serum ferritin (µg/L, mean ± SD)			
At the last visit	1642.2 ± 1908.7	1745.6 ± 1978.4	680.2 ± 374.5
1-year mean ± SD	1652.0 ± 990.6	1728.2 ± 1859.8	873.1 ± 568.8
5-years mean ± SD	1617.9 ± 962.0	1718.1 ± 1858.3	660.8 ± 397.8
Age at first endocrinology consultation (years ± SD)	24.7 ± 0.9	24.2 ± 7.8	31.4 ± 6.5
Reason for endocrinology consultation, n (%)			
Regular visit	63 (61.2%)	55 (59.1%)	8 (89.0%)
Delayed puberty and/or hypogonadism related	21 (20.4%)	20 (21.5%)	1 (11.0%)
Calcium metabolism and/or osteoporosis related	6 (5.8%)	6 (6.4%)	-
Growth retardation	6 (5.8%)	6 (6.4%)	-
Abnormal glucose metabolism	3 (2.9%)	3 (3.2%)	

n, number; RBC, red blood cell.

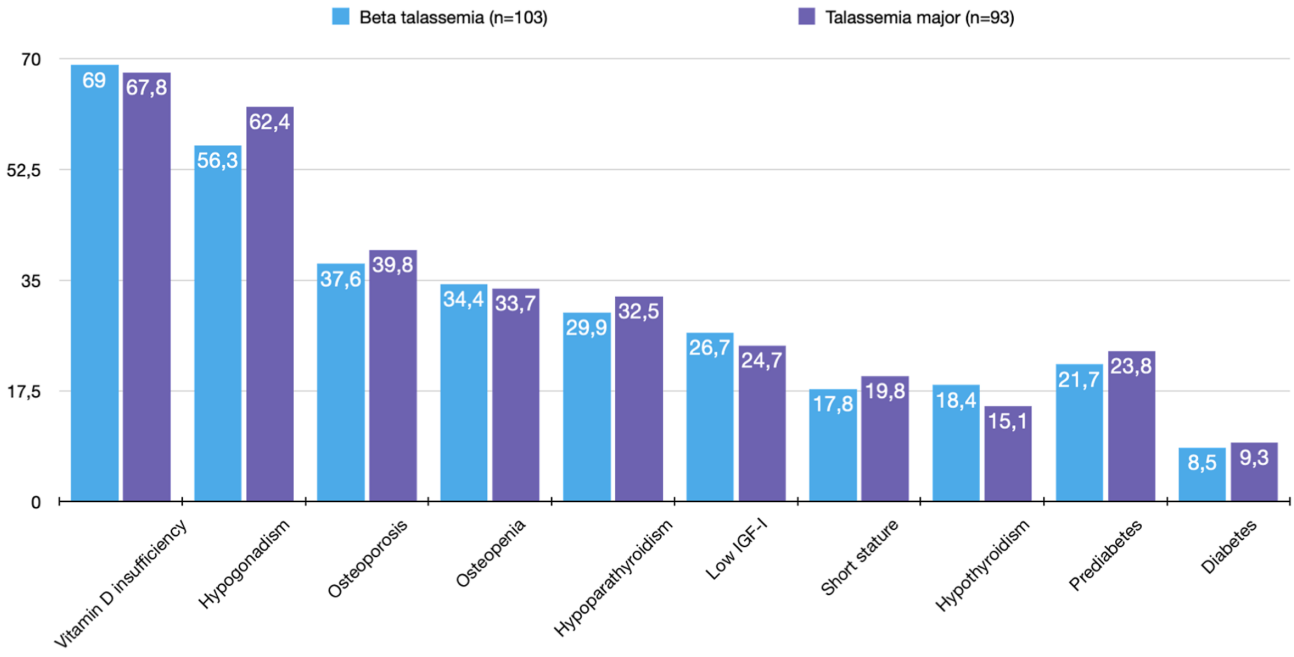

Figure 1. The frequency (%) of endocrine–metabolic disorders in beta-thalassemia patients.

Table 2. Comparison of Parameters of Patients With and Without Hypogonadism

	Patients with Hypogonadism (n = 58)	Patients Without Hypogonadism (n = 45)	*P*
Hb (g/dL)	9.3 ± 1.0	9.9 ± 1.2	**.028**
Ferritin at the last clinic visit (µg/L)	2019.4 ± 2283.8	1156.0 ± 1122.4	**.014**
5-years calculated mean ferritin (µg/L)	2001.4 ± 2201.0	1090.7 ± 761.1	**.006**
Myocardial MRI T2-star (msec)	22.5 ± 11.6	28.8 ± 8.4	**.002**
Liver MRI T2-star (msec)	4.2 ± 5.1	5.2 ± 4.6	.34
Total hip BMD (g/cm^2)	0.798 ± 0.152	0.904 ± 0.139	**.002**
Femur neck BMD (g/cm^2)	0.735 ± 0.295	0.879 ± 0.129	**.007**
Lumbar total BMD (g/cm^2)	0.924 ± 0.170	0.970 ± 0.107	.15

All variables were presented as mean ± SD. $P < .05$ was considered statistically significant. Significant *P*-values are given in bold.
Hb, hemoglobin; BMD, bone mineral densitometry; MRI, magnetic resonance imaging.

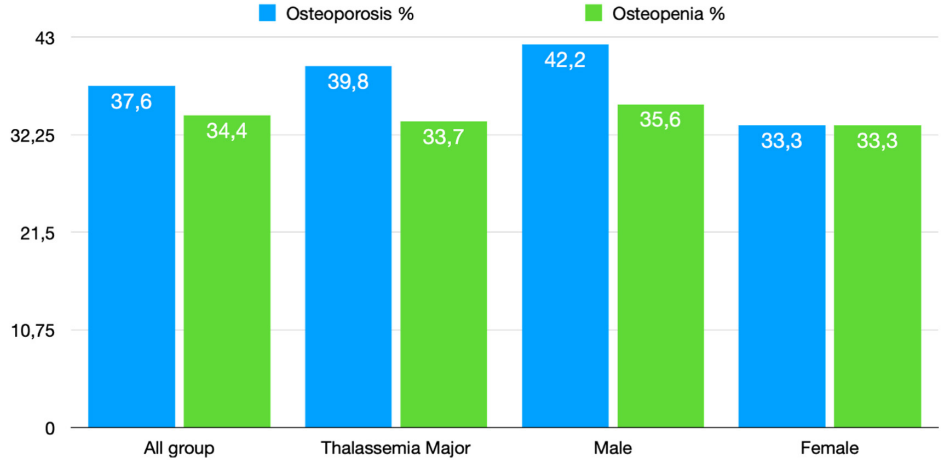

Figure 2. The frequency of osteoporosis and osteopenia in beta-thalassemia patients.

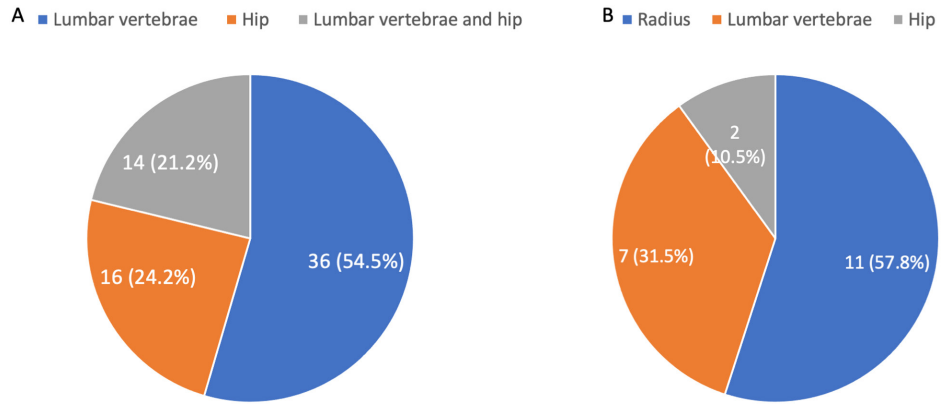

Figure 3. (A) The sites of osteoporosis/osteopenia in the overall study population. (B) The locations of pathological fractures.

osteoporosis/osteopenia in the overall population and the locations of pathological fractures.

Osteoporotic patients were older at the time of study enrollment (32.9 vs. 30.0 years, $P=.018$). Male patients had a higher prevalence of osteoporosis (42.2% vs. 33.3%, $P=.37$) and pathological fractures (22.4% vs. 16.0%, $P=.41$), though the differences were statistically insignificant. Patients with hypogonadism (51.0% vs. 21.4%, $P=.003$), diabetes mellitus (75.0% vs. 35.1%, $P=.027$), and short stature (64.7% vs. 32.0%, $P=.012$) had higher rates of osteoporosis. However, the ages at the time of the diagnoses of hypogonadism and diabetes were unrelated to these associations. In addition, both IGF-1 and GH levels were lower in patients with osteoporosis, yet the difference was only significant for IGF-1 (IGF-1: 65.6 ± 38.4 ng/dL vs. 100.5 ± 68.8 ng/dL, $P=0.004$; GH: 0.26 ± 0.07 ng/dL vs. 1.34 ± 0.74 ng/dL, $P=.14$). Contrarily, smoking, vitamin D deficiency, hypoparathyroidism, and prediabetes were not associated with osteoporosis. Ferritin and hemoglobin (Hb) concentrations and MRI T2-star values were comparable among patients with and without osteoporosis.

A total of 20 patients had at least 1 pathological fracture (19.4%). The radius was the most common site for pathological fractures, followed by vertebrae and hip (Figure 3B). Pathological fractures were more common in patients who smoked (36.4% vs. 15.3%, $P=.037$) and had hypogonadism (28.1% vs. 7.1%, $P=.02$). Patients with pathological fractures were shorter than patients without (155.8 ± 10.9 cm vs. 160.7 ± 9.7 cm, $P=.038$). Diabetes or any of the other endocrine disorders or thalassemia-related parameters (e.g., ferritin, MRI T2-star) were not linked to pathological fractures.

Primary Hypoparathyroidism

Primary hypoparathyroidism was common in beta-thalassemia patients, characterized by significantly lower PTH (18.1 ± 7.4 pg/mL vs. 36.4 ± 22.2 pg/mL, $P=.001$) and serum corrected Ca levels (8.5 ± 0.6 mg/dL vs. 9.2 ± 0.3 mg/dL, $P=.001$), but comparable serum *P* levels (4.5 ± 1.2 mg/dL vs. 4.1 ± 0.8 mg/dL, $P=.057$). Females had a marginally higher rate (34.0% vs. 22.5%, $P=.36$) of hypoparathyroidism compared to male patients. The concentrations of 25OHD were comparable ($P=.33$). Height, BMD, ferritin, Hb, and MRI T2-star measurements did not differ between patients with and without hypoparathyroidism.

Short Stature

Short stature was found in 18% of the patients with beta-thalassemia, with male patients having a slightly higher prevalence (21.6% vs. 14.0%, $P=.32$). About 1 in every 5 patients had short stature in the thalassemia major group (Figure 1). The GH levels in patients with short stature were significantly lower (0.93 ± 1.03 ng/dL vs. 1.81 ± 2.7 ng/dL, $P=.036$), whereas IGF-1, thyroid function tests, Hb, ferritin, and MRI T2-star measurements were all similar. None of the patients in the thalassemia intermedia group had a history of GH treatment as children, whereas 3/88 (3.4%) of those in the thalassemia major group had a history of GH treatment in childhood.

Hypothyroidism

Hypothyroidism was present in 19 subjects (5 with thalassemia intermedia, 14 with thalassemia major), with 11 receiving levothyroxine replacement. The mean age at hypothyroidism diagnosis was 27.3 ± 8.2 years in the whole group but younger in patients with thalassemia major (24.4 ± 7.4 years vs. 35.6 ± 3.0 years, $P=.005$). Other endocrine–metabolic disorders or thalassemia-related parameters were not associated with thyroid hormone status.

Diabetes Mellitus and Prediabetes

Diabetes mellitus and prediabetes were found in 8/86 (9.3%) and 20/84 (24%) of the patients with thalassemia major, respectively, but not in the patients with thalassemia intermedia. Prediabetes was identified in 12 subjects as impaired fasting glucose, 3 as impaired glucose tolerance, and 5 as both. The mean age at diagnosis of either diabetes or prediabetes was 25.9 ± 7.3 years. Seven diabetic patients required insulin treatment; 6 received basal–bolus insulin, and 1 received basal insulin. Metformin was given to the remaining patient.

Patients with diabetes had higher rates of osteoporosis, with lower lumbar (0.814 ± 0.140 g/cm^2 vs. 0.960 ± 0.145 g/cm^2, $P=.033$) and total hip (0.643 ± 0.111 g/cm^2 vs. 0.862 ± 0.148 g/cm^2, $P=.001$) BMD measurements. There was no such difference between patients with and without prediabetes.

Regarding thalassemia-related parameters, there was a positive correlation between calculated mean ferritin levels over 5 years and FPG ($r=0.29$, $P=0.004$) as well as 75 g OGTT second-hour glucose levels ($r=0.46$, $P=0.001$). The Hb or MRI T2-star measurements, on the other hand, were not associated with these variables.

Hypocortisolemia

Before enrolling in the study, 2 patients were diagnosed with adrenal insufficiency (1.9%) and had been on glucocorticoid replacement since they were 16 and 20 years old, respectively. Based on basal ACTH and cortisol measurements, 22 patients (21.3%) in the overall group

opted for a 250 µg intravenous tetracosactide stimulation test during the evaluations. Fifteen of them (15/22, 68.2%) agreed to be tested, and 4 of them were found to have subclinical hypocortisolemia.

New-Onset Endocrine Disorders During Follow-Up

Fifty and 34 patients had 3- and 5-year follow up, respectively. Eight out of 50 patients (16%) developed a new endocrine disorder in 3 years, while 4 out of 34 (12%) in 5 years. All patients had at least 1 endocrine disorder at baseline. Gender, age, number of existing endocrine disorders, ferritin and Hb concentrations, or MRI T2-star measurements were not associated with developing a new endocrine–metabolic disorder.

In 3 years of follow-up, 2 patients with prediabetes developed overt diabetes mellitus (2/20, 10%), both diagnosed with a 75 g OGTT. Meanwhile, 2 additional patients established prediabetes. In addition, osteoporosis was detected in 3 patients, all who had hypogonadism at baseline assessment. Hypogonadism and hypoparathyroidism developed in 1 patient each. One patient developed multiple new endocrine disorders, including prediabetes, osteoporosis, and subclinical hypothyroidism. In 5 years of follow-up, 3 patients were diagnosed with osteoporosis; 2 had hypogonadism at baseline. The remaining patient developed hypothyroidism.

Discussion

In this study, we presented the endocrine–metabolic disorders observed in 103 adult patients with beta-thalassemia at a tertiary health-care center in Turkey. Vitamin D deficiency was the most common endocrine disorder, while hypogonadism and osteoporosis/osteopenia were the most common endocrine complications. Patients with hypogonadism exhibited higher ferritin levels, lower hemoglobin concentrations, and increased myocardial iron deposition. Additionally, there was a positive correlation between 5-year calculated mean ferritin levels and FPG and 75 g OGTT second-hour glucose levels. Patients with hypogonadism and diabetes had higher rates of osteoporosis. Hypogonadism was also associated with pathological fractures. Otherwise, the remaining endocrine disorders were not related to thalassemia-related parameters or each other. Long-term follow-up revealed new-onset endocrine disorders in a small percentage of patients. Osteoporosis and prediabetes/diabetes were the most commonly identified conditions.

The patients with beta-thalassemia had a mean age of around 25 years at their first visit to the endocrinology clinic, though it ranged from 7 to 47 years. Because many patients came to our center from various other centers, the age of endocrine referral for all patients could not be confirmed through the hospital information system; some were based on patient statements. This might be one of the causes of the comparatively advanced age at the time of the first endocrinology visit. However, there may also be a delay in patients with beta-thalassemia being referred to endocrinology clinics. We observed that only 60% of the study participants were referred for routine endocrinological evaluation. Given the high prevalence of endocrine–metabolic disorders in this population, endocrinology visits should be a part of transitional care for these patients as they transition from pediatric hematology to adult hematology clinics.

Most of our study population had more than one endocrine–metabolic complication, with 42% having three or more. De Sanctis et al[18] and Shamshiraz et al[19] also reported the occurrence of multiple endocrine complications (≥3) in patients with beta-thalassemia; however, the rates were relatively low, at only 7.5% and 10%, respectively. Poor compliance with iron chelators was the main significant difference between patients with multiple endocrine complications and those with none, though serum ferritin levels were comparable.[18] Although we did not investigate our cohort regarding iron chelator compliance, our results reveal that the 2 groups had similar 5-year calculated mean ferritin levels. The relatively higher incidence of ≥3 endocrine–metabolic complications in our cohort may be attributed to the older age of our patients compared to the cohort studied by Shamshiraz et al.[19] Additionally, De Sanctis et al[18] did not report osteoporosis in their study.

The prevalence of vitamin D deficiency has ranged from 0% to 80% in studies including patients with thalassemia major and/or intermedia.[20] This variability, at least in part, may be attributed to differences in the definition of vitamin D deficiency used across these studies and the age and region of the included patients. Our findings are consistent with previous research that indicated a significant prevalence of vitamin D deficiency (67.8%) in patients with thalassemia major but no association between vitamin D and BMD measurements.[21,22] However, the relationship between osteopenia/osteoporosis and vitamin D status and whether vitamin D replacement improves BMD measurements in these patients remains controversial.[20]

Osteoporosis and pathological fractures are significant endocrine complications in thalassemic adults, with prevalence rates reaching up to 69% and 44%, respectively.[21,23-26] Several studies reported that the lumbar vertebrae have predominantly been affected,[23,26] as in our study. On the other hand, pathological fractures were recorded mainly in the radius in our cohort, which is consistent with some[27] but not all studies.[28] However, there is still debate over the significance of vitamin D.[20,21] Another point of contention in thalassemia-related osteoporosis is whether it is associated with serum ferritin levels. Some studies establish a connection between the two, while others do not.[23,28,29] Our study aligns with the latter group, as we did not show a relationship between serum ferritin levels and BMD measurements. Even if no direct relationship exists between serum ferritin levels and osteoporosis, it has been demonstrated that effective iron chelation treatment with deferasirox can improve BMD in the long term.[24,25]

Hypogonadism is frequently observed in beta-thalassemic patients. It has been reported as the most common endocrine complication of thalassemia in several studies,[5,30] including ours, but not all studies.[31] Importantly, we observed that hypogonadism was associated with low hemoglobin concentrations, higher serum ferritin levels, and increased myocardial iron overload, consistent with previous research.[32,33] Hence, our study supports the view that early initiation of iron chelators and consistent adherence to these agents may play a key role in preventing hypogonadism. Furthermore, hormone replacement treatment in hypogonadal patients with beta-thalassemia is essential to osteoporosis treatment.[34] Nonetheless, patients with thalassemia major may still be at risk for developing endocrine–metabolic complications despite efficient iron chelation.[35]

In our study, except for hypogonadism, we found no correlation between serum ferritin levels, Hb concentrations, cardiac or liver MRI T2-star measurements, and endocrine complications. However, several studies indicated a correlation between serum ferritin levels and/or MRI T2-star measurements in the liver and myocardium and the development of thalassemia-related endocrine complications

such as hypothyroidism and diabetes.[6,7,36,37] On the other hand, our findings support the findings of Zervas et al,[38] who observed no link between serum ferritin levels and thyroid functions in patients with thalassemia major. Also, Kanbour et al[39] found that the rate of endocrine complications was similar between patients with and without severe hepatic iron overload, except impaired fasting glucose was more common in patients with very high hepatic iron concentrations. Our study found a positive correlation between 5-year mean ferritin levels and FPG and OGTT second-hour glucose. However, ferritin levels were comparable between patients with and without glucose metabolism disorders. While the correlation was not strong with FPG ($r = 0.29$, $P = .004$), it still may indicate clinical significance. The fact that serum ferritin level is an indirect indicator of iron deposition in the organism might have diminished the strength of the correlation. Furthermore, additional studies reported a relationship between elevated serum ferritin levels and diabetes mellitus.[6,7]

A few studies evaluated the development of new-onset endocrine complications during the long-term follow-up of adult beta-thalassemic patients.[24,25,40,41] We observed that 16% and 12% of patients developed a new endocrine–metabolic complication in 3 and 5 years of follow-up, respectively. Our findings indicate that endocrinologists should be particularly watchful for the development of glucose metabolism disorders and osteoporosis in adult thalassemic patients during long-term follow-up. We did not observe a link between serum ferritin levels or cardiac and liver iron accumulation and the development of new endocrine complications. This observation aligns with the findings of some,[24,41] but not all, studies.[25] Although Pinto et al[41] similarly found no correlation between myocardial or liver MRI T2-star values and the development of glucose metabolism disorders, their study revealed a correlation with pancreatic iron accumulation, which we did not evaluate in our patients.

Our study has several limitations. Firstly, it is a single-center study involving a limited number of participants, particularly those with long-term follow-up. However, our center is an experienced university hospital with a longstanding history of following and treating beta-thalassemia patients. Secondly, we have not evaluated our cohort's compliance with iron chelator therapy. We instead calculated long-term mean ferritin levels to gain insight into their treatment adherence. Also, the forms of iron chelator modalities were not considered in assessing thalassemia-related endocrine–metabolic complications.

In conclusion, this comprehensive study evaluated the landscape of endocrine–metabolic disorders in adult patients with beta-thalassemia at an experienced tertiary health-care center in Turkey. The occurrence of multiple endocrine complications was frequent. Vitamin D deficiency emerged as the predominant disorder, with hypogonadism and osteoporosis/osteopenia being the most common complications. Hypogonadism was correlated with higher ferritin levels, low hemoglobin concentrations, and increased myocardial iron deposition. Also, our findings highlighted a significant link between 5-year calculated mean ferritin levels and glucose metabolism parameters. Otherwise, there was no correlation between thalassemia-related parameters and endocrine–metabolic complications. Furthermore, these parameters did not predict the development of new endocrine complications. Endocrinologists should pay special attention to the emergence of glucose metabolism disorders and osteoporosis among adult thalassemic patients during long-term follow-up. Our findings support that all patients with thalassemia major, regardless of their ferritin levels, should be evaluated for the development of endocrine complications.

Ethics Committee Approval: This study was approved by Ethics Committee of Hacettepe University (Approval No: GO 20/874, Date: 06.10.2020).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

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