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ORIGINAL ARTICLE – OPEN ACCESS

Relationship Between Endocrinopathies and Ferritin Levels in Adult Turkish Patients with Beta Thalassemia Major: A Single-Center Experience

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ABSTRACT

Objective: Despite regular transfusions and iron-chelation therapies, endocrine complications still remain an important cause of morbidity in patients with beta thalassemia major (BTM). We aimed to evaluate the relationship between endocrine complications and serum ferritin levels in adult patients with BTM.

Materials and Methods: The endocrine test results of adult patients with BTM were retrospectively reviewed. Normality testing was performed using the Shapiro–Wilk test. For the analysis, we used an independent samples t-test when parametric test assumptions were met; otherwise we used Mann–Whitney U test. A p value of <0.05 was considered statistically significant.

Results: A total of 66 adult patients with BTM. (female: 56.1%, male: 43.9%, mean age: 25.8±6.6 years) were evaluated. The mean ferritin level was 1504.9±861 ng/ml (range 304–5464 ng/ml). Of the patients, 60.6% had endocrinopathy. The rates of hypogonadism was 51.5%, hypothyroidism was 16.7% (subclinical hypothyroidism: 13.6%, central hypothyroidism: 3.03%), hypoparathyroidism was 10.6%, diabetes mellitus was 7.6%, vitamin D insufficiency was 40.9%, vitamin D deficiency was 33.3%, low bone mass was 56.1%, and that of low IGF-1 was 57.6%. We found a significant relationship between ferritin levels and the presence of hypogonadism, low bone mass, and low IGF-1 levels (p<0.001). Patients used higher doses of deferasirox due to iron overload (p<0.001). Patients needed higher deferasirox doses to decrease ferritin levels.

Conclusion: Among adult patients with BTM, endocrinopathies were prevalent in patients with elevated ferritin levels. Patients with BTM should undergo regular testing for endocrine disorders, and ferritin levels must be kept under control.

Keywords: Thalassemia, adult, endocrinopathy, ferritin

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INTRODUCTION

Beta thalassemia major (BTM) is a congenital hemoglobinopathy. Mutations in the beta-globin chains result in chronic hemolytic anemia and the need for regular blood transfusions, which constitutes a significant health problem. The leading treatment approaches include regular and sufficient erythrocyte transfusions and iron-chelation therapy (1, 2).

The complications that can be observed in thalassemia occur in relation to the disease itself or to the administered therapies. The most common complications affecting the patients' life span are related to the transfusions (iron overload). Complications, such as endocrine disorders (hypogonadism, diabetes mellitus, hypothyroidism, growth retardation, osteoporosis), heart disease, chronic liver disease, thrombophilia and infections, etc., can also be observed (3, 4). In patients with BTM, morbidity and mortality rates considerably decreased due to an effective iron-chelation therapy. Complications are inevitable in patients who receive regular transfusions, but undergo insufficient chelation therapy. Improvements in the treatment options for patients with thalassemia have increased life spans. However, endocrinopathies are still the most significant complications that could affect the patients' quality of life (5–7). The present study thus evaluates endocrine complications in adult Turkish patients with BTM.

MATERIALS and METHODS

We conducted a retrospective registry study. A total of 66 adult patients with BTM were followed-up in Denizli State Hospital. The age, gender, height, weight, transfusion interval, hemoglobin, platelet count and biochemical test results, insulin-like growth factor-1 (IGF-1), calcium, phosphorous, albumin, vitamin D, parathyroid hormone (PTH), thyroid stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, testosterone, and ferritin levels of the patients were retrieved from the archived records. A fasting blood glucose >126 mg/dL and a postprandial blood glucose level >200 mg/dL were defined as diabetes mellitus (DM). IGF-1 levels were evaluated according to age- and gender-specific reference ranges.

Table 1a. Demographic data and laboratory findings of 66 patients with thalassemia major

Mean/Median	Male Mean (n=29)	Male Median (n=29)	Female Mean (n=37)	Female Median (n=37)	Normal range
Age	25.2±6.8	22	26.3±6.4	26	
Height (cm)	161.0±4.3	160	153±5.4	152	
Weight (kg)	50.1±4.4	50	45.8±6.8	43	
BMI (kg/m^2)	19.2±1.2	19	19.4±1.8	19	20–25
Transfusion interval (day)	21.4±0.7	21	21.5±0.8	21	
Hemoglobin (g/dL)	9.2±0.6	9.2	9.3±0.4	9.4	Male: 13–16.5 Female: 12–16
Ferritin (ng/mL)	1597±996	1467	1432±774	1202	Male: 30–300 Female: 15–150

BMI: Body mass index

We regularly evaluated all the patients at every visit, during which transfusion and chelator therapies were planned. We evaluated ferritin levels every 3 months. Furthermore, endocrine tests were routinely conducted every 6 months. Additionally, we consulted the results to the department of endocrinology. The blood samples of the patients were collected in the morning, whereas blood samples of female patients were obtained during the menstrual period to evaluate FSH, LH, etc. Biochemical analyses were performed using the Abbott Architect i2000 Autoanalyzer.

We defined subclinical hypothyroidism as a TSH level >4 mlU/L with normal fT4 levels. Bone mineral density (BMD) was determined from an X-ray absorptiometry (DXA) of the lumbar vertebrae and hip. Since the patients were young, we used z scores to determine the bone mass. Z scores were determined as SDs from an age- and sex-matched population. Z score ≥−2 was considered normal, whereas a Z score<−2 indicated a low bone mass. We defined vitamin D deficiency as serum 25(OH)D in concentrations <20 ng/mL, and a vitamin D insufficiency as a serum 25(OH)D concentration of between 20 and 30 ng/mL.

Patients with hypocalcemia, hyperphosphatemia, and decreased or inappropriately normal PTH levels were considered to have primary hypoparathyroidism. We evaluated the mean of serum ferritin levels within the last 24 months. Serum ferritin level ranged from normal to 300 ng/mL. We defined iron overload as an increase in the ferritin level, exceeding 1000 ng/mL in patients. A diagnosis of hypogonadism was established based on the basal FSH, LH, estradiol, and testosterone levels, together with the clinical findings of the patients (delayed sexual development, short stature, decreased libido, inability to have a child, menstrual disturbances, etc.).

The data was analyzed using SPSS Statistics version 25 software. The results were presented as mean±SD and median (min–max values). For normality testing, we used the Shapiro–Wilk test. When parametric test assumptions were met, we used the independent samples t-test; otherwise we used the Mann–Whitney U test. A p value of <0.05 was considered statistically significant. No procedures were performed and no interventions were made during this study due to the retrospective study design.

We obtained an informed consent from all patients. The ethics Committee of the Pamukkale University Faculty of Medicine approved the study. Number of decision was 60116787-020/77268, dated November 20, 2017.

RESULTS

The study included 66 patients with BTM, including 29 males (43.9%) and 37 females (56.1%). The mean age was 25.8±6.6 years (range 18–43 years). The mean transfusion interval was 21.5±0.8 days (range 20–24 days). The mean serum ferritin level was 1504.9±861 ng/mL (range 304–5464 ng/ml). Of the total, 40 patients (60.6%) had undergone splenectomy. The mean height was 165.3±3.8 (158–174) cm in males and 153.7±5.0 (145–170) cm in females. We found a short stature in 40 patients (60.6%). The demographic data and laboratory findings are shown in Table 1a and 1b.

The mean age of onset of the iron-chelation therapy was 6.6±5.23 (2–19) years and median age was 5 years. Patients with BTM did not use an iron chelator therapy regularly in the past. They did not receive this therapy because of the difficulty in accessing the drug. According to our records, they received therapy regularly for the last 10 years. Fifty-five patients (83.3%) had used deferasirox, six patients (9.09%) had used deferasirox and desferrioxamine, three patients (4.54%) had used deferiprone, and two patients (3.03%) had used deferiprone and desferrioxamine as part of their iron chelator therapy (Table 2). The mean deferasirox dose was 1463.1±497.5 mg (range 500–2250 mg).

At least one endocrinopathy was detected in 40 patients (60.6%). The rates of hypogonadism was 51.5%, hypothyroidism was 16.7% (subclinical hypothyroidism: 13.6%, central hypothyroidism: 3.03%), hypoparathyroidism was 10.6%, DM was 7.6%, vitamin D insufficiency was 40.9%, vitamin D deficiency was 33.3%, low bone mass was 56.1%, and low IGF-1 was 57.6%. The relationship between endocrine complications and ferritin level is presented in Table 3a.

We found a significant relationship between serum ferritin (Table 3a) levels and the presence of endocrine complications (p<0.001). We detected different deferasirox doses in patients with or without

Table 1b. Other laboratory tests

	Mean±SD	Normal range	Median /(min.–max.)
FSH (mlU/mL)	4.2±2.8	Folicular phase: 4–10 (female), 1–19 (male)	3.25 (0–11.2)
LH (mlU/mL)	3.3±2.9	Folicular phase: 2–10 (female), 1–9 (male)	2.97 (0–17.1)
TSH (mlU/L)	2.48±1.25	0.4–4	2.21 (0.58–7)
Estradiol (pg/mL female)	41.5±34.1	Folicular phase: 27–122 (female)	31.8 (0.1–127)
Testesterone (ng/mL male)	2.6±2.3	1–7.8	1.02 (0–6.8)
PTH (ng/L)	46.2±22.9	15–65	45.2 (7.2–141)
Calcium (mg/dL)	9.1±0.4	8.5–10.2	9.2 (7.9–10.2)
Phosphor (mg/dL)	4.0±0.5	2.5–4.4	4.1 (2.5–5.3)
Vitamin D (ug/L)	24±8.9	>30	19.5 (3.5–39)
IGF-1 (ng/mL)	101.2±43.1	>115	87.65 (13.8–211)

FSH: Follicle stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid stimulating hormone; PTH: Parathyroid hormone; IGF-1: Insulin-like growth factor-1; SD: Standard deviation; min.: Minimum; max.: Maximum

Table 2. Use of chelator therapy

Chelator	n	%
Deferasirox	55	83.3
Desferrioxamine and deferasirox	6	9.09
Deferiprone	3	4.54
Desferrioxamine and deferiprone	2	3.03

endocrinopathies (p<0.001). There is an indirect relationship between endocrinopathies and iron chelator therapies (deferasirox, deferiprone, etc.) Among the patients with BTM, serum ferritin levels were higher in those with endocrinopathies than in those without endocrinopathies. Patients needed higher deferasirox doses to decrease ferritin levels (Table 3b). Even though we used maximum doses of deferasirox, 42 of 66 patients' ferritin levels were above 1000 ng/mL. Patients with endocrinopathies had higher ferritin levels and they used higher doses of deferasirox.

We defined hypogonadism by evaluating FSH, LH, estradiol, and testosterone levels. Of the 66 patients with BTM, 34 (51.5%) were found to have hypogonadism: 16 (47%) males and 18 (52.9%) females. In addition, 28/34 (82.3%) of the patients had a delayed sexual development. Moreover, 12 of 18 (66.6%) female patients

Table 3a. The relationship of serum ferritin and endocrinopaties

Endocrinopaties	Ferritin (ng/mL) Mean±SD	p
Hypogonadism (n=34)+	2058.02±835.68	<0.001
Hypogonadism (n=32) -	917.34±345.06	
Hypothyroidism (n=11)+	1647.09±700.27	=0.306
Hypothyroidism (n=55)-	1476.54±892.52	
Hypoparathyroidism (n=7)+	1467.85±464.09	=0.636
Hypoparathyroidism (n=59)-	1507.14±910.85	
Diabetes mellitus (n=5)+	1894.40±552.00	=0.136
Diabetes mellitus (n=61)-	1473.04±877.00	
Vitamin D insufficiency/deficiency (n=49)+	1546.09±942.07	
Vitamin D insufficiency/deficiency (n=17)-	1401.05±626.87	=0.745
Low bone mass (n=37)+	1963.70±867.20	<0.001
Normal bone mass (n=29)-	919.68±348.12	
Low IGF-1 levels (n=38)+	1958.00±844.20	<0.001
Normal IGF-1 Levels (n=28)	890.14±356.65	

SD: Standard deviation; IGF-1: Insulin-like growth factor-1

Table 3b. Relationship between deferasirox dose and the presence of endocrinopathies

	Deferasirox dose (mg)		
	Mean±SD (+)	Mean±SD (-)	p
Endocrinopathy (+/-) (n=36/n=35)	1715.2±401.5	1100±388.6	<0.001
Hypogonadism (+/-) (n=32/n=29)	1812.5±290.9	1077.5±378.5	<0.001
Bone mineral density (low/normal) (n=36/n=25)	1812.5±282.6	960±235.8	<0.001
IGF-1 (low/normal) (n=37/n=24)	1709.4±388.7	1083.3±401.5	<0.001

SD: Standard deviation; IGF-1: Insulin-like growth factor-1

had primary amenorrhea, and 6 (33.3%) of 18 patients had other menstrual disturbances. Furthermore, 25/34 (73.5%) of the patients had a short stature, and 29/34 (85.2%) of them had decreased libido. No patients with hypogonadism had a child. In patients with hypogonadism, the mean estradiol level was 13.0±8.7 pg/mL and the mean testosterone level was 0.5±0.3 ng/mL. We found a significant relationship between ferritin levels and the presence of hypogonadism ($p<0.001$).

Of the total, nine patients (13.6%) had subclinical hypothyroidism and two (3.03%) had central hypothyroidism, making a total of 11 patients with hypothyroidism (16.7%). In addition, five patients (7.6%) had DM and seven (10.6%) had hypoparathyroidism. No significant relationship was found between ferritin levels and hypothyroidism, DM, or hypoparathyroidism ($p>0.05$). Also, no significant relationship was found between ferritin levels and TSH and fT4 levels ($p>0.05$). Of the total, 27 patients (40.9%) had a vitamin D deficiency and 22 patients (33.3%) had a vitamin D insufficiency. However, we did not find a relationship between 25(OH)D levels and ferritin levels ($p>0.05$). The mean calcium and phosphorus levels were 9.1±0.4 mg/dL and 4.0±0.5 mg/dL, respectively. The mean 25(OH)D and PTH levels were 24±8.9 ug/L and 46.2±22.9 ng/L, respectively.

BMD was normal in 29 patients (43.9%) and low in 37 patients (56.1%). The mean Z score was −1.18±1.68 (range −3.3±0.9). Ferritin levels were higher in patients with a lower bone mass. We detected a considerable difference in ferritin levels between the patients with normal BMD and those with low BMD ($p<0.001$). We detected higher ferritin levels in patients with a lower bone mass. We found relationships between low bone mass and vitamin D deficiency/insufficiency ($p=0.047$), hypothyroidism ($p=0.011$) and hypogonadism ($p=0.001$). We did not identify a relationship between low bone mass and hypoparathyroidisim ($p=0.061$).

We found IGF-1 levels to be below the lower limit of normal in 38 patients (57.6%). The mean level of IGF-1 was 101.2±43.1 ng/mL. A significant relationship was found between ferritin levels and IGF-1 levels ($p<0.001$). Higher ferritin levels were detected in patients with low IGF-1 levels than in patients with normal IGF-1 levels.

Limitation

Our study is a retrospective study. The study included the first author's patients in the mandatory service period in Denizli State Hospital. The absence of T2 magnetic resonance is the limitation of our study. In addition, we evaluated the BMD only by using DXA. We did not evaluate impaired glucose tolerance.

DISCUSSION

Endocrine complications still constitute a significant cause of morbidity in patients with BTM (8). Even though the patients in the present study received regular transfusions with a mean transfusion interval of 21.5±0.8 days, and iron chelating therapies over the last 10 years, endocrinopathies was detected. We discovered a significant relationship between serum ferritin levels and the presence of endocrinopathies.

Vitamin D deficiency/insufficiency was noted in 74.2% cases in our study. In previos studies, the rate of vitamin D deficiency/insufficiency in patients with BTM was reported to be in the range of 37%–78.2% (1, 9–13). The findings of the present study are consistent with those of previous studies. İn the general population, vitamin D deficiency is common because of the life style (14). The rate of vitamin D deficiency/insufficiency in patients with BTM was similar to that of the general population. Patients with BTM must receive vitamin D replacement on a regular basis.

In this study, hypogonadism was detected in a total of 34 patients (51.5%), while the rate of hypogonadism among patients with BTM in previous studies was in the range of 46.8%–76%. Our findings are similar to those reported in previous studies (2, 15, 16). High ferritin levels in patients with BTM is an important risk factor for hypogonadism (17–19). We identified a significant relationship between ferritin levels and the presence of hypogonadism ($p<0.001$). Patients should be evaluated in terms of hypogonadism if they have high ferritin levels. Therefore, gonadal tests (FSH, LH, estradiol, testosterone) and ferritin levels must absolutely be followed-up in all patients. Patients with hypogonadism should be consulted at endocrine clinic for hormone replacement therapy.

The rates of subclinical hypothyroidism and central hypothyroidism were 13.6% and 3.03%, respectively in the present study, with an overall hypothyroidism rate of 16.7%. No patient had overt hypothyroidism. Our findings are similar to those reported in previous studies. Dhouib et al. (20) in their study reported the rate of hypothyroidism to be 18%. In the study by Haghpanah et al. (21), the rate of hypothyroidism was identified as 22.9%. Of their patients, 19.9% had subclinical hypothyroidism and 1% had central hypothyroidism. One must keep in mind the possibility of central hypothyroidism, although it is a rare complication in patients with BTM. The rate of hypoparathyroidism in the present study was reported as 10.6%. Similar to our findings, the reported rate of hypoparathyroidism in previous studies ranges from 8.5% to 11.1% (17, 22). Thyroid and parathyroid evaluation should be regularly performed in all patients. Central hypothyroidism is a rare state, which should be kept in mind.

The rate of DM was 7.6% in the present study, whereas the rate of DM in previous studies ranged between 7% and 16.1% (2, 23, 24). These reports are similar to our findings. No significant relationship was found between ferritin levels and hypothyroidism, DM or hypoparathyroidism. This may be linked to the small number of patients and the prevalence of complications. Nevertheless, DM is a serious complication causing morbidity in BTM patients. For this reason, a close watch is necessary.

We detected low bone mass in 56.1% of the patients. The rate of low bone mass (Z score<−2) in previous studies was reported to be in the range of 50.7%–61.1% (25, 26). The findings of the present study are similar to those of previous studies. We found a significant difference in terms of serum ferritin levels between patients with normal BMD and patients with low bone mass ($p<0.001$). Toxic effects of iron in osteoblasts could cause a decrease in the bone mass, thus careful evaluation of ferritin levels is required. Low bone mass is an important reason for morbidity in patients with BTM (19), but the etiology of low bone mass are multifactorial (hypogonadism, ineffective erythropoietic activity, hypothyroidism, physical activity, zinc deficiency, vitamin D deficiency etc.) in pa-

tients with BTM (27). In this study, we discovered the relationships between low bone mass and vitamin D deficiency/insufficiency, hypothyroidism and hypogonadism. BMD should be followed at regular intervals with DXA. If low bone mass is detected, it should be treated not only for low bone mass, but also for the etiology of low bone mass.

We found low IGF-1 levels in 57.6% of the patients. Previous studies have reported 50%–67% of patients with low IGF-1 levels, similar to the findings of the present study (28, 29). Iron overload, chronic anemia, chronic liver disease, nutrition, hypothyroidism, and hypogonadism are all factors that contribute to growth hormone deficiency in patients with BTM (19, 27, 28). That being said, the presence of a significant relationship between ferritin levels and IGF-1 levels of the patients is a remarkable finding. Records of ferritin levels should be kept regularly. However, IGF-1 levels were affected by many factors, therefore, testing IGF-1 levels alone is not sufficient to evaluate the growth hormone status in adult patients with BTM.

We found that there is an indirect relationship between endocrinopathy and iron chelator therapies (deferasirox, deferiprone, etc.). Among the BTM patients, serum ferritin levels were higher in those with endocrinopathies than those without endocrinopathies. Higher doses of deferasirox were needed by patients to decrease ferritin levels. Even though we used maximum doses of deferasirox, 42 of 66 patients levels of ferritin were above 1000 ng/ml. Therefore, we found increased endocrinopaties. Patients with endocrinopaties had higher ferritin levels and they used higher doses of deferasirox. Endocrinopaties could occur in spite of using maximum doses. Patients with endocrinopaties could need higher doses of deferasirox to decrease higher ferritin levels.

To conclude, endocrine complications remains a matter of concern, despite the use of iron chelator therapies in adult patients with BTM. The present study showed that patients with BTM and elevated ferritin levels are at a greater risk of endocrinopathies. Patients with BTM should undergo regular and close follow-up for endocrine complications. Hormone replacement therapies must be managed in collaboration with endocrinologists. Ferritin levels must be controlled with iron chelator therapies.

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