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Original Article

Leptin and thyroid hormones in beta-thalassemia major: A cross-sectional study

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Abstract

Background: Hypothyroidism and leptin deficiency are two common endocrinopathies in β-thalassemia major patients (β-TM). Changes in leptin levels may lead to changes in thyroid hormone levels in thalassemia patients through suppression of the hypothalamus-pituitary-thyroid axis. Hence, we aimed to evaluate their correlation in β-TM patients.

Methods: A cross-sectional study was conducted on transfusion dependent β-thalassemia patients receiving chelation treatment between 2018 and 2019. Tri-iodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), and leptin were measured for each participant. Data analyzed by SPSS, $p < 0.05$ was considered as significant.

Results: One hundred and twenty-six β-TM patients aged between 10 and 30 years old participated in the study, including 55 (43.7%) females and 71(56.3%) males. TSH abnormality was prevalent among 13 (23.6%) females and 10(14.1%) males. Leptin level was significantly lower in males (6.65±7.27 VS 2.41±2.79, $p<0.01$). TSH was correlated with leptin in all ($r=0.393$, $p<0.01$), females ($r=0.387$, $p<0.01$), males ($r=0.387$, $p<0.01$), adolescents ($r=0.512$, $p<0.01$), young adults ($r=0.287$, $P=0.01$), underweights ($r=0.483$, $p<0.01$) and normal weight ($r=0.301$, $P=0.03$) thalassemia patients. T4 was correlated with leptin in all ($r=0.201$, $p=0.02$), females ($r=0.281$, $P=0.03$), males ($r=0.281$, $P=0.03$), and adolescents ($r=0.280$, $P=0.03$) β-TM patients. T3 did not correlate with leptin in all groups of the patients.

Conclusion: In summary, leptin levels were significantly lower in males, and TSH abnormality was common in both genders. Therefore, screening for endocrine issues may benefit these people. Furthermore, leptin exhibited a correlation with TSH and T4. This may support the role of leptin on thyroid function in β-TM patients.

Keywords: Leptin, Thyroid hormones, Hypothyroidism, Thalassemia major.

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β-thalassemia, a common single-gene mutation disorder, leads to the reduction or absence of β-globin chain production in red blood cells (RBC) (1, 2). The natural selection is the major contributor of the high prevalence of β-thalassemia in *Plasmodium falciparum* endemic regions such as the Mediterranean, the Middle-East, Indian subcontinent, and the Far East (3, 4). The number of carriers is estimated to be 1.5% of the population (5). Approximately 40,000 infants are annually born with β-thalassemia disorder. Twenty-five thousands of them are thalassemia transfusion dependent (TDT) for the rest of their life (6). Iran is located in the thalassemia belt, and holds about 25,000 β-thalassemia major (β-TM) individuals and three million carriers that commonly reside in the Persian Gulf and the Caspian shoreline (7, 8). β-thalassemia has a spectrum encompassing β-thalassemia minor, intermedia, and major.β-TM is the most severe form that needs regular transfusion for survival (2, 4).

The need for regular transfusion is related to ineffective erythropoiesis and hemolytic anemia, which result from insoluble α-globin particles called hemi chromes within RBCs (9, 10). Although the administration of iron chelators prevents excessive iron overload in these patients, predominantly the liver, heart, and endocrine glands are at risk of iron deposition and later parenchymal dysfunction (11). Hypothyroidism is one of the endocrine disorders that is prevalent among β-TM patients (12, 13). Forty-eight β-TM patients were followed-up for 12 years. Thirty-five percent of them developed overt hypothyroidism. Ninety-four percent of hypothyroidism cases occurred at age ten or older (14). Hypothyroidism in β-TM patients is associated with iron overload. Specifically, individuals with ferritin levels exceeding 7000 ng/mL are at a higher risk of developing overt hypothyroidism between the ages of 2 and 10 (15). Leptin is a 16kda hormone that plays a role in energy balance within the body (16).

Leptin attaches to its receptors in arcuate nuclei and activate the hypothalamus-hypophysis axis increasing thyroid hormone secretion and energy expenditure. Hence, whenever leptin levels decrease in starvation or similar circumstances thyroid hormones level also decline (17). Leptin levels drops in β-TM patients due to iron overload (18, 19). Additionally, free thyroxine (T4) levels are lower in β-TM patients compared to healthy controls (20). Moreover, T4 is positively associated with leptin level in circulation (19, 21). Therefore, we hypothesized that hypothyroidism may be secondary to the abnormality of leptin secretion caused by iron overload. Hence, we aimed to assess the association between leptin levels and thyroid hormones in β-TM patients.

Methods

Participants: One hundred and twenty-six participants were enrolled in this cross-sectional study. We recruited the participants from all the patients admitted to Ali ibn Abi Talib Hospital and Ali Asghar pediatric clinic, from October 2018 to October 2019. Patients between the ages of 10 and 30 with a confirmed diagnosis of β-TM, who required blood transfusions and received chelating agents as part of their treatment, were included in the study. Patients with a history of irregular blood transfusions before the age of 2 years, hemoglobin (Hb) levels below 9 g/dL in subsequent referrals for transfusion, and a duration of less than five years for receiving chelation therapy were excluded from the study. The definite diagnosis of β-thalassemia major for all patients was established based on Hb-electrophoresis results. Absence of HbA, HbF of 92-95%, and Hb A2 of 5-8% was defined as β-thalassemia major (22). Current study was a part of a comprehensive project aimed to evaluate interlukine-6, tumor necrosis factor α and leptin in thalassemia patients. The study was approved by the Ethics Committee of Zahedan University of Medical Sciences (ethical code of IR.ZAUMS.REC.1400.307.) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Consent forms were obtained from the participants or their guardians after the study approval.

Data collection: The patient's height (cm) and weight (kg) were measured by a stadiometer and scale with light clothes and without shoes. BMI was calculated based on the formula: BMI= (Weight (Kg))/(Height (m^2)). All patients were tested for serum thyroid hormones tri-iodothyronine (T3), T4, thyroid stimulating hormone (TSH), and leptin. Three milliliters of blood were collected from each subject, followed by centrifugation of the samples at 3000 g for 10 minutes at 5°C. Then separated serum was stored in a refrigerator at -20°C. A 250-micron serum sample was then separated and analyzed for thyroid hormones by Diaplus Inc. using the ELISA method (USA), and other serum samples were analyzed for leptin levels by Diagnostic Biochem using the ELISA method (Canada).

Statistical analysis: Data were analyzed using SPSS22.00 (SPSS Inc, Chicago, IL, USA). Data were reported as mean±standard deviation and range for continuous variables or number and percentage for categorical variables. The distribution of the quantitative variables was tested using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare freely distributed variables between two groups. The Pearson correlation coefficient was used to determine the correlation between two variables.

Results

A total of 126 β-TM patients with a mean age of 16.64±6.32 years old (range: 10 to 30) participated in the study, including 55 (43.7%) females and 71 (56. 3%) males. The participants distributed by age 20 into 56 (44.4%) adolescents and 70(55.6%) young adults. According to BMI, participants were 77 (61.1%) underweight and 49 (38.9%) normal weight. The clinical data had free distribution, leptin (K. S= 0.275, p <0.01), height (K. S= 0.097, p <0.01), weight (K. S= 0.089, P =.01), age (K. S= 0.094, p <0.01), TSH (K. S= 0.250, p <0.01), T4 (K. S= 0.085, P=0.02) and T3 (K. S= 0.374, p <0.01). The mean height and weight of the patients were 149.94±13.61cm and

40.93±10.59 Kg, respectively. The mean levels of TSH, T4, T3, and leptin were as follows: 4.05±4.95 µIU/mL (range: 0.4-38) for TSH, 8.00±2.35 µg/dL (range: 3.50-20.70) for T4, 1.27±1.07 ng/mL (range: 0.8-13) for T3, and 4.26±5.62 ng/ml (range: 0.14-33.40) for leptin. According to the cutoff of 5 µIU/ml for TSH, the TSH abnormality was prevalent among 13 (23.6%) females and 10 (14.1%) males. The results of Mann-Whitney U test showed that females had significantly higher leptin levels than males (6.65±7.27 VS 2.41±2.79, p<0.01). However, no significant differences exist in TSH (P=0.08), T4 (P=0.43), and T3 (P=0.23) between the two genders. Moreover, adolescents had significantly higher T3 compared to young adults (1.44±1.59 VS 1.13±0.19, P=0.01); howbeit, there were no differences in TSH (P=0.78), T4 (P=0.16), and leptin (P=0.34) between adolescents and young adults. In addition, underweights exhibited higher plasma levels of T3 compared to normal weight (1.37±1.36 VS 1.11±0.19, p<0.01); however, there were no difference in TSH (P=0.34), T4 (P=0.62), and leptin (P=0.29) between these two groups.

Table 1 shows the comparison of paraclinical and anthropomorphic indices across sex, age, and BMI classification. The results of Pearson coefficient test showed that TSH was correlated with leptin in total (r=0.393, p<0.01), females (r=0.387, p<0.01), males (r=0.387, p<0.01), adolescents (r=0.512, p<0.01), young adults (r=0.287, P=0.01), underweights (r=0.483, p<0.01) and normal weight (r=0.301, P=0.03) thalassemia patients. T4 was correlated with leptin in total (r=0.201, P=0.02), females (r=0.281, P=0.03), males (r=0.281, P=0.03), and adolescents (r=0.280, P=0.03) β-TM patients. T3 had no significant correlation with leptin in thalassemia patients (r=0.071, P=0.42). Table 2 shows the correlation between leptin, TSH, T4, and T3 in all and in the different subgroups of patients.

Table 1. Comparison of anthropomorphic indices, thyroid hormones and leptin across sex, age, and BMI classification

Variable	Gender			Age			BMI		
	Male	Female	P	Adolescent	Young adult	P	Underweight	Normal	P
Height cm	151.13±13.09	148.40±14.23	0.368	141.48±13.41	156.70±9.37	<0.001	145.82±14.43	156.41±9.10	<0.001
Weight Kg	41.17±10.32	40.62±11.02	0.676	34.30±8.84	46.23±8.76	<0.001	35.49±8.50	49.47±7.48	<0.001
TSH µIU/mL	3.17±2.26	5.17±6.91	0.085	3.95±4.80	4.12±5.10	0.787	3.60±4.18	4.76±5.93	0.341
T4 µg/dL	7.82±2.01	8.23±2.73	0.430	8.42±2.69	7.66±2.00	0.162	8.14±2.55	7.78±2.00	0.624
T3 ng/mL	1.36±1.42	1.15±0.19	0.233	1.44±1.59	1.13±0.19	0.011	1.37±1.36	1.11±0.19	0.006
Leptin ng/mL	2.41±2.79	6.65±7.27	<0.001	4.21±6.49	4.31±4.87	0.346	4.08±5.97	4.54±5.07	0.290

Footnote: Mann-whitney U test was performed to compare continuous variable between two groups. Abbreviations: TSH, thyroid stimulating hormone; T4, thyroxine; T3, tri-iodothyronine; BMI, body mass index.

Table 2. Correlation of leptin with TSH, T4 and T3 in all and different categorizations of thalassemia patients

Leptin	N	TSH		T4		T3	
		r	p	r	p	r	p
All	126	0.393	<0.001	0.201	0.024	0.071	0.428
Females	55	0.387	0.003	0.281	0.038	0.035	0.798
Males	71	0.387	0.003	0.281	0.038	0.035	0.798
Adolescent	56	0.512	<0.001	0.280	0.036	0.076	0.577
Young adults	70	0.287	0.016	0.097	0.423	0.151	0.212
Underweight	77	0.483	<0.001	0.221	0.053	0.073	0.528
Normal weight	49	0.301	0.036	0.166	0.255	0.112	0.442

Footnote: TSH, thyroid stimulating hormone; T4, thyroxine; T3, tri-iodothyronine.

Discussion

In the current study, leptin levels were lower in males than females. Moreover, TSH abnormalities were more common in females than males. Furthermore, leptin positively correlated with TSH and T4 in β-TM patients. This association between leptin and TSH remained significant in males, females, adolescents, young adults, underweight, and normal-weight patients. Leptin was also associated with T4 separately in males, females, and adolescents. Shahramian, et al (18) discovered that leptin levels were lower in β-TM patients than controls. Consistent to the current study, they also found leptin levels are significantly lower in male than females. Additionally, Harbi, et al. (23) revealed leptin level is significantly lower in thalassemia major patients compared to thalassemia minor and healthy controls. Haghpanah, et al. (24) published a systematic review and meta-analysis in 2021. In line with the current study, thyroid dysfunction was common in β-TM patients. The pooled prevalence of sub-clinical and overt hypothyroidism in TDT was 16.22%, which is close to the prevalence of 18.3% found in our study. Additionally, the results revealed ferritin levels were significantly higher in hypothyroid patients than euthyroid individuals, proving the pivotal role of iron overload in hypothyroidism in β-TM patients.

By reviewing the literature, we realized that there has not been much study on the association between leptin levels and thyroid hormones in β-TM patients. Shahramian, et al. (21) conducted a cross-sectional study on 90 children with β-TM aged 6-16 years old. The results revealed a positive association between T4 and leptin levels in β-TM patients. These results are in line with our findings that leptin had a positive correlation with the level of free T4. The results regarding the association of TSH and leptin are controversial. Inconsistent with the study, Shahramian, et al.'s study (21) showed that leptin had no association with TSH levels in β-TM children. Dayer et al.'s (25) also conducted a study on 30 β-TM patients and 24 healthy subjects aged 12-20 years old. They found no association between TSH levels and leptin in case and controls. The current study has two advantages over previous studies that may reduce the type II error, including recruiting more participants and a broader age spectrum.

Two hypotheses regarding this correlation of TSH and T4 with leptin can be proposed. First, there is a causal relationship between the two hormones, and the decline in one lead to the decrease of the other. There is evidence that leptin physiologically, through the arcuate pathway in the hypothalamus, may act on the paraventricular nuclei, which is the center of production of thyroid-releasing hormone (TRH), which in turn control the secretion of TSH and T4 (26, 27). Reducing leptin secretion due to decrement of energy reserves, starvation as an example, suppresses the hypothalamus-pituitary-thyroid axis (17). Studies that measure leptin levels in β-TM patients indicated that leptin serum levels are lower than controls (23, 28). Hence, we assume low leptin levels conveys the message to the hypothalamus of β-TM patients that the energy sources of the body cannot supply a high metabolic rate, so the thyroid hormone synthesis should be suppressed. There is similar evidence that supports the role of inappropriate secretion of leptin on delayed puberty in β-TM children. Perrone, et al. (29) concluded that fat tissues cannot maintain adequate leptin secretion when the highest level of leptin is required for puberty in thalassemia patients. Indeed, appropriate leptin secretion transmits to the hypothalamus that energy reserves are adequate for reproduction. Hence, insufficient secretion of leptin leads to hypogonadotropic hypogonadism (30).

The second hypothesis is that no cause-and-effect relationship between the two hormones does exist, but a common factor affects both. In other words, iron deposition in the endocrine tissues of patients with β-TM leads to both hypothyroidism and leptin deficiency at the same time, causing a significant correlation between the two hormones (15, 31). There is evidence for and against these hypotheses. The studies state that central hypothyroidism is the common thyroid disorder among β-TM patients, supporting the role of leptin deficiency in suppressing the hypothalamus-hypophysis-thyroid axis (14, 32); however, studies found primary or subclinical hypothyroidism as the prevalent form (15, 33), are in favor of iron overload as the cause of hypothyroidism, and support the second hypothesis. Hence, our findings support the first hypothesis due to the positive correlation discovered between TSH and leptin levels.

The main limitation that we faced was the cross-sectional nature of the study, which does not determine the cause-and-effect relationship between the two hormones that have been established to have an association with each other. We proposed to researchers in the field of hematology who work in the thalassemia endemic areas to conduct a longitudinal study among β-TM patients with leptin deficiency for ten years from the first years of teenage to the first years of young adulthood to determine whether the leptin deficiency is the trigger for hypothyroidism or not. We also suggest conducting a clinical trial on hypothyroid β-TM patients for future studies to measure the effect of leptin in treating clinical and subclinical hypothyroidism compared to the placebo group. In summary, leptin levels were significantly lower in males than females. Moreover,

TSH abnormality was more common in females than males. Therefore, regular screening for endocrine issues may benefit these people. Furthermore, leptin exhibited a correlation with TSH and T4. This may support the role of leptin in regulating thyroid function in β-thalassemia major patients.

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Conflict of interests: None to declare.

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