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RESEARCH ARTICLE
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Hormones and metabolic parameters among a sample of beta Thalassemia major patients in Aqrah city- Iraq

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ABSTRACT

Background: Inconveniently, many physicians still emphasize the anemia of thalassemia patients, overlooking the problems of iron overload and its consequences on the development of the child.

Objectives: The main aim of this study is to assess the serum levels of thyroid and parathyroid hormones, calcium, phosphorus, and vitamin D3 among Beta-thalassemia patients.

Methods: Sixty children with thalassemia major with a ratio of males to females 1.222, were included from the 1st of May 2022 to the 15th of July 2022. A detailed medical history is obtained from every patient, and a clinical examination is performed. Blood samples were taken for Hb, thyroid and parathyroid hormones, serum calcium, phosphorous, and vitamin D3.

Results: The mean age (SD) was 11.4 (4.1) years and the largest proportion 25 (41.7%) were aged 10-14 years. Nine children had high TSH (15%), high T4 6 (10%), low PTH 5 (8.3%), low D3 57 (95%), high phosphorus 43 (71.7%), low calcium 28 (46.7%), high ALP 57 (95%), and high ferritin 60 (100%). Half of the children had short stature.

There were significant positive correlations detected between the duration of the disease and variables like ferritin, TSH, and Phosphorus, while the correlation with PTH and height for age were all negative. The mean of TSH among children aged > 10 years (5.05 mIu/ml) was significantly higher than the mean of children aged ≤ 10 years (3.42 Miu/ml). In comparison; the mean of PTH of children aged ≤ 10 years (29.39 pg/ml) was significantly higher than the mean PTH of children aged ≤ 10 years (19.97 pg/ml). No significant differences regarding D3, calcium, ALP, and phosphorus were detected.

Conclusions: Endocrine complications are major health issues in thalassemia despite the medical therapies.

Keywords: *Beta-thalassemia, stunting, anemia, TSH, and PTH*

INTRODUCTION

Thalassemia is an autosomal recessive disorder characterized by a defect in the formation of alpha- or beta-globin chains, leading to ineffective erythropoiesis and hemolytic anemia. Despite thalassemic patients are usually asymptomatic or only mildly anemic, the severe type needs a lifelong blood transfusion.1 Beta thalassemia major is often presented between the ages of 4 and 6 months, owing to a high level of hemoglobin F at birth that gradually drops over the first year of life.2 Clinical manifestations are anemia, short stature, cardiac failure, organomegaly, disorders of bone metabolism, signs of extramedullary hematopoiesis and endocrinopathies.3 In Iraq, hemoglobinopathies affect 6-10% of the population, and thalassemia constitutes the main part.4 A study among Erbil University students unveiled a carrier incidence of 7.7%.5 In the Duhok governorate, 3.7% of married couples were found to be beta-thalassemia carriers during testing for premarital health screening.6 Without treatment, patients with beta-thalassemia major die in early childhood. The foundation of main stem treatment is regular blood transfusions that successfully prolong life expectancy in addition to adequate chelation therapy. Frequent blood transfusions may lead to iron overload and excessive iron deposition in different organs such as the liver, heart, lungs, and endocrine glands. Secondary hemosiderosis continues to be a major challenge, affecting the function of many organs in the body including endocrine disturbances.7 Iron chelators have increased survival rates,8 but endocrine problems have increased in frequency and consequently have a major impact on quality of life.9 The prevalence of hypothyroidism in Beta Thalassemia Major (BTM) patients ranges from 6 to 30 percent in different nations.7 Infiltration of the thyroid gland, ongoing tissue hypoxia, damage from free radicals, and organ hemosiderosis are the major causes of thyroid dysfunction. The symptoms of hypothyroidism though non-specific can affect many organ systems, hence an annual laboratory evaluation of thyroid function is recommended in all beta thalassemic.10 Thalassemic patients on regular blood transfusion have been known to develop hypoparathyroidism, particularly beyond the age of 10 years. In several studies frequency of hypoparathyroidism in beta-thalassemia patients was found to be between 2.5% to 40%.11,12 Parathyroid hormone is the main regulator for calcium-phosphate metabolism and thus bone turnover.13 Hypoparathyroidism may lead to severe osteoporosis and many other manifestations such as paresthesia, carpopedal spasm, tetany, and seizures.14 These symptoms are augmented more by inadequate levels of vitamin D. The majority of thalassemic patients have an insufficient level of vitamin D.15 In this study, we aimed to assess the serum levels of thyroid, parathyroid hormones, vitamin D3, calcium, and phosphorus, and examine the association of abnormal profiles with demographic features and haematological and biochemical markers.

MATERIALS AND METHODS

A cross-sectional study was carried out in the Akre thalassemia center at Gulan Hospital in Akre City- north of Iraq from the 1st of May 2022 to the 15th of July 2022. The study protocol and ethical approval were obtained from the research ethics committee of the Kurdistan Higher Council of Medical Specialists before starting the research. All records of beta thalassemia major patients aged 5-18 years were studied at the Akre thalassemia center. A total of 79 patients identified their data were collected and analyzed. All participants were informed of the study objectives and then recruited after providing informed consent directly or through parents. Nineteen patients either refused to participate or were excluded due to other comorbidities like Heart failure, Diabetes, liver disease, and Renal failure or consumed multivitamins and minerals for the last 3 months. The response rate was 60 (73.2%). A questionnaire was used to address all relevant patients' demographic data, duration of disease, family history of haematological and endocrine disorders, blood transfusions history, and chelating therapy chronological history. Patient height in (cm) and weight in (kg), were measured by all participants and adjusted for age according to world health organization criteria (WHO). All patients who had clinical consultation and completed the clinical examinations, then they were asked to provide a

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blood sample under fully aseptic conditions. Serum biochemical parameters including hemoglobin, calcium, phosphorus, vitamin D3, alkaline phosphatase, total serum bilirubin, ferritin, thyroid-stimulating hormone, free thyroxin, and parathyroid hormone were obtained for all patients. Immediately after the blood samples were taken, calcium was measured using the ion-specific electrode (ISE) potentiometric method. Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). Numerical and categorical data were analyzed. An unpaired student t-test was used to compare the means of the two groups. Spearman rho correlation coefficient was used to calculate the strength of correlation. The Z score for patient demography was extracted using Anthro plus statistical software of the WHO. Clinical and subclinical hypothyroidism were recorded with hypocalcemia if serum Ca is less than 8.5 mg/dL. The phosphate level was adjusted for age.

RESULTS

Sixty children were included in the study. Their mean age (SD) was 11.4 (4.1) years, the median was 11.7 years, and the age range was 5-18 years. The largest of the children proportion 25 (41.7%) were aged 10-14 years, and the ratio of males to females is 1.222. More than half of the children (55%) were living in rural areas. More than one-third 23 (38.3%) of the children were in stage II and 18 30% were in stage I. Other details are presented in Table I.

TABLE I. Basic characteristics of children.

	No.	%	Mean	SD	Median	Min.	Max
Phosphorus mmol/l			1.8	0.6	1.6	1.1	4.0
Normal	17	28.3					
High	43	71.7					
T3 nmol/l			3.5	10.8	1.8	0.6	85.0
Low	2	3.3					
Normal	47	78.3					
High	11	18.3					
T4 nmol/l			93.1	36.8	88.7	1.6	235.0
Low	7	11.7					
Normal	47	78.3					
High	6	10.0					
TSH mlu/ml			4.4	3.7	3.7	0.5	25.3
Normal	51	85.0					
High	9	15.0					
Parathyroid hormone pg/ml			23.6	11.0	22.6	4.6	59.2
Low	5	8.3					
Normal	55	91.7					
D3 ng/ml			14.4	6.9	13.6	2.3	39.8
Low	57	95.0					
Normal	3	5.0					
CRP			4.3	2.9	4.0	0.4	15.1
Normal	47	78.3					
High	13	21.7					
Last Hb g/dl			8.2	0.9	8.2	6.0	10.3
Low	60	100.0					
New Hb g/dl			8.6	0.8	8.4	7.1	10.5
Low	60	100.0					
MCV			75.3	9.6	76.3	7.9	87.1
Low	20	33.3					

Normal	40	66.7					
WBC			8.2	4.9	6.7	4.3	28.0
Low	60	100.0					
Platelets			363.0	201.8	289.0	150.0	955.0
Normal	43	71.7					
High	17	28.3					
Calcium mg/dl			8.8	0.9	8.6	7.4	11.4
Low	28	46.7					
Normal	29	48.3					
High	3	5.0					
ALP U/l			236.0	93.5	213.0	86.0	535.0
Normal	3	5.0					
High	57	95.0					
TSB mg/dl			2.0	1.3	1.6	0.4	7.6
Normal	14	23.3					
High	46	76.7					
Last ferritin ng/ml			4069.9	3005.7	3287.5	307.0	13810.0
High	60	100.0					
New ferritin ng/ml			4788.2	4228.8	3362.0	475.0	20000.0
High	60	100.0					

Around two-thirds, (63.3%) of patients were of medium socioeconomic status, and only 8.3% of children were of high socioeconomic status (Figure 1).

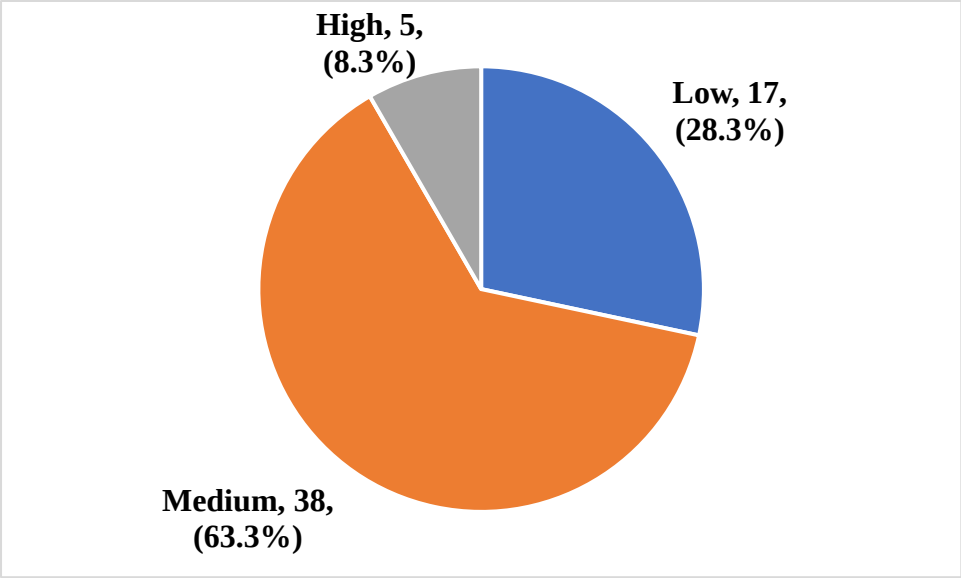

FIGURE 1: Socio-economic status of families.

The number and percentage of children with abnormal values are as follows: high phosphorus 43 (71.7%), high T3 11 (18.3%), High T4 4 (10%), High TSH 9 (15%), low parathyroid hormone 5 (8.3%), low D3 57 (95%), high CRP 13 (21.7%), low Hb 60 (100%), low MCV 20 (33.3%), low WBCs 60 (100%), high platelets 17 (28.3%), low calcium 28 (46.7%), high ALP 57 (95%), high TSB 46 (76.7%), high ferritin 60 (100%). The details are presented in Table II.

TABLE II: Hematological parameters.

	No.	%	Mean	SD	Median	Min.	Max
Phosphorus mmol/l			1.8	0.6	1.6	1.1	4.0
Normal	17	28.3					
High	43	71.7					
T3 nmol/l			3.5	10.8	1.8	0.6	85.0
Low	2	3.3					
Normal	47	78.3					
High	11	18.3					
T4 nmol/l			93.1	36.8	88.7	1.6	235.0
Low	7	11.7					
Normal	47	78.3					
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TSH mlu/ml			4.4	3.7	3.7	0.5	25.3
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Parathyroid hormone pg/ml			23.6	11.0	22.6	4.6	59.2
Low	5	8.3					
Normal	55	91.7					
D3 ng/ml			14.4	6.9	13.6	2.3	39.8
Low	57	95.0					
Normal	3	5.0					
CRP			4.3	2.9	4.0	0.4	15.1
Normal	47	78.3					
High	13	21.7					
Last Hb g/dl			8.2	0.9	8.2	6.0	10.3
Low	60	100.0					
New Hb g/dl			8.6	0.8	8.4	7.1	10.5
Low	60	100.0					
MCV			75.3	9.6	76.3	7.9	87.1
Low	20	33.3					
Normal	40	66.7					
WBC			8.2	4.9	6.7	4.3	28.0
Low	60	100.0					
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New ferritin ng/ml			4788.2	4228.8	3362.0	475.0	20000.0
High	60	100.0					

Half of the children had stunting (indicated by low height for age Z score of less than -2 Z). Table III shows that 10% of children had BMI for age Z score of less than -3 .

TABLE III: Anthropometric parameters (categories).

	No.	(%)
Height for age Z		
< -3	12	(20.0)
-2.1 to -3	16	(26.7)
-1.1 to -2	20	(33.3)
Zero to -1 Z	11	(18.3)
> zero	1	(1.7)
BMI for age Z		
< -3	3	(5.0)
-2.1 to -3	3	(5.0)
-1.1 to -2	15	(25.0)
Zero to -1	16	(26.7)
> zero	23	(38.3)
Weight for age Z		
< -3	11	(18.3)
-2.1 to -3	12	(20.0)
-1.1 to -2	21	(35.0)
Zero to -1	13	(21.7)
> zero	3	(5.0)
Total	60	(100.0)

The descriptive statistics of anthropometric parameters are presented in Table IV. It is evident that half of the children had a Z score height for age of -1.97, and half of the children had a BMI for age Z score of less than -0.46 (Table IV).

TABLE IV: Descriptive statistics of anthropometric parameters.

	Height for age Z score	BMI for age Z
Mean	-2.05	-0.51
Standard deviation	1.19	1.24
Minimum	-5.10	-4.00
Maximum	0.24	1.56
25th percentile	-2.89	-1.31
50th percentile (median)	-1.97	-0.46
75th percentile	-1.12	0.58

A significant positive correlation was detected between the duration of the disease and the following variables: ferritin, CRP, TSB, TSH, and Phosphorus, while there was a negative significant correlation with parathyroid hormone (PTH), height for age Z score, and BMI for age Z score (Table V).

TABLE V: Correlation between the 'duration of the disease' with the studied variables.

	Rho	(p)
Hb g/dl	0.022	(0.869)
Ferritin	0.296	(0.022)
WBC	0.150	(0.254)
CRP	0.334	(0.009)
ALP U/I	0.046	(0.730)
PLT	0.107	(0.415)
TSB mg/dl	0.295	(0.022)
PTH pg/ml	-0.521	(< 0.001)
TSH mIu/ml	0.293	(0.023)
T3 nmol/ml	-0.303	(0.018)
T4 nmol/ml	-0.093	(0.482)
D3_ng_ml	-0.063	(0.630)
Phosphorus mmol/L	0.327	(0.011)
Calcium	-0.220	(0.091)
Height for age Z score	-0.509	(< 0.001)
BMI for age Z score	-0.364	(0.004)

The mean TSH level among children aged more than 10 years (5.05 mIu/ml) was significantly higher than the mean TSH level of children aged ≤ 10 years (3.42 mIu/ml) (p = 0.045), while the mean PTH level of children aged ≤ 10 years (29.39 pg/ml) was significantly higher than the mean PTH level of children aged less than 10 years (19.97 pg/ml) (p = 0.001). There were no statistical differences between the two groups in the p-value of the D3, Ca+, ALP, and phosphorus (Figure 2).

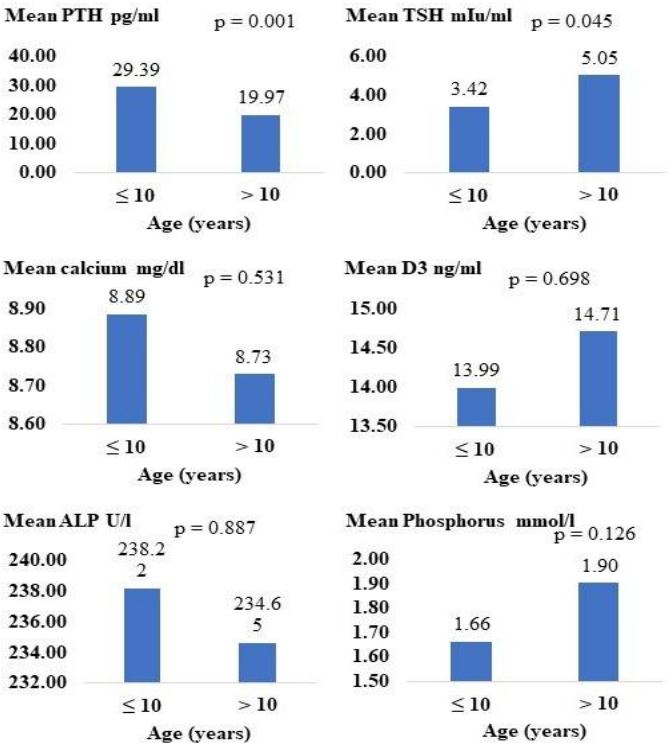

FIGURE 2: Means of some metabolic parameters by age.

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DISCUSSION

Although blood transfusion methods and chelation therapy have significantly increased patient survival among those with thalassemia over the past several decades, long-term blood transfusion-related problems continue to have a substantial impact on this population's quality of life. Our study aimed to evaluate thyroid and parathyroid in chronically transfused children with beta-thalassemia major in the first and second decades of life.

Our sample size constitutes of two groups; the 1st group of children belong to the first decade 22 (36.7%) and the 2nd group of children 38 (63.3%) belong to the second decade of life. The main aim of our study is to analyse the prevalence of thyroid dysfunction and its association with the duration of the disease and the number of blood transfusions as well as serum ferritin level, and adequacy of chelation. Iron deposition from repeated transfusions has been implicated as the likely mechanism causing thyroid dysfunction in BTM patients.

Our data analysis found thyroid dysfunction in 11 children (18.3%). This is close to what was reported in Tabriz by Najafpour et al. (16%).16 Other studies reported some differences. Hypothyroidism was found in 7% by Karamifar,17 whereas, De Sanctis reported 21.6% in Italy.18 Subclinical hypothyroidism was the most common type observed in our study; in 5 children (8.3%), followed by overt hypothyroidism in 4 patients (6.7%), while 2 children (3.3%) were diagnosed with central hypothyroidism. This is similar to previous studies by Sharma et al. and Abdel-Razek et al. where subclinical hypothyroidism was most frequently reported. 19,20 However, Seow CE Et al. observed that 63.6% of hypothyroidism patients had a central mechanism.21

In this study, all of the hypothyroid children except one (90.9%) were aged over 10 years. This was similar to results found by Toumba M. et al.22 Upadya et al. reported in his cohort study 43% hypothyroidism in the first decade of life.23 Differences in samples and ages of patients, in addition to genetic, cultural, and economic factors as well as the frequency and the quality of blood transfusion and chelators may contribute to the variations in different studies. Not surprisingly, a significant correlation was noticed between thyroid dysfunction and the duration of the disease, unlike other research, which found no correlation between the duration of the disease and thyroid problems.24

We did not find any relevance between hypothyroidism and serum ferritin like many other studies, 17,21,25 but others believe there is. 23 Despite published reports relating endocrine dysfunction to iron overload, it was recently demonstrated that the degree of iron overload, at least reflected by serum ferritin levels, was not associated with the development of endocrine complications.26

The lack of a connection between serum ferritin and hypothyroidism may be explained by claiming that the damage to the endocrine glands prompted by chronic hypoxia is more severe than the harm caused by hemosiderosis as well as the fact that serum ferritin does not obtain an accurate reflection of iron overload in the previous years.

The absence of the relationship between ferritin and hypothyroidism may be explained by suggesting that the damage to endocrine glands caused by chronic hypoxia is more pronounced than that caused by hemosiderosis as a consequence of the collapse of iron in addition to that serum ferritin doesn’t obtain accurate reflection of iron overload in the previous years.

All of the study's participants underwent an anthropometric assessment, which revealed that 23 (38.3%) of them were underweight and 28 (46.7%) were stunted for their age (Table I). For instance, in Shiraz, 40% of patients were reported to be wasting while 59% of females and 51% of men were observed to be short stature. 17 Whereas B. Moiz et al. observed that 42% of the patients were malnourished (BMI z-score 2) and that 65% of patients were short-stature. 27 De Sanctis et al. evaluated the prevalence rate of short stature among 3023 β thalassemia patients in 16 countries. The prevalence was 53%. 28

Parathyroid dysfunctions are thought to be a rare consequence of iron overload seen in beta-thalassemia and are observed as hypoparathyroidism, accompanied by other

endocrinopathies. In our series, we measured also serum Ca, P, ALP, PTH, and vitamin D3 levels to assess parathyroid dysfunction in these patients. We found that low parathyroid hormone (hypoparathyroidism) in 5 (8.3%) patients, low serum total calcium in 28 (46.7%) patients, while high phosphorous and ALP levels in 43 (71.7%) and 57 (95%) patients, respectively. The analysis of vitamin D3 levels, although it was taken during the summer, was markedly low in 57 (95%) patients. These findings indicate damage to the parathyroid gland.

In a few published studies, the prevalence varies greatly from very low (7.6 %) to as high as 20%. 29,25 The largest study on endocrine problems in thalassemia published included 3817 patients from 29 centers, and it recorded hypoparathyroidism in 6.9% of patients, although the percentage varied from center to center. 30 The ages of all hypoparathyroidism patients in our study were older than 10 years. Pirinccioglu et al. found that hypoparathyroidism mostly appeared in the second and third decades of life in transfusion-dependent thalassemia patients, just as we observed in our cases. 31

It was observed that no clear association between hypoparathyroidism and serum ferritin levels. Other studies also found no correlation between hypoparathyroidism and serum ferritin levels. 32,33 Mahmoud et al. reported that hypoparathyroidism is related to high serum ferritin levels. 24 The reason why some patients develop parathyroid dysfunction and others do not; is not exactly known. It is thought that parathyroid dysfunction is not always related to iron level, but to some other factors based on the patient's tendency. Several possible mechanisms have been described to be responsible for the damage of parathyroid glands through iron overload. These include free radical formation and lipid peroxidation resulting in mitochondrial, lysosomal, and sarcolemmal membrane damage. 34

High serum phosphorus levels in our series were analogous to studies that reported significantly higher serum phosphorous levels in thalassemic patients than in the control groups, 35 On the contrary, some researchers reported that phosphorous levels were within the normal range in patients compared to controls. 36

Low serum 25-hydroxy vitamin D levels have also been reported previously in β-thalassemic patients by many investigators. 37,38 This deficiency has been attributed to the malabsorption of vitamins as well as inadequate dietary intake.39,40 Another plausible explanation is hepatic dysfunctions which lead to defective hydroxylation of vitamin D resulting in decreased levels. 41 Other authors also reported that the etiology of 25-OH-D deficiency might be the hepatic iron overload rather than the dysfunction of endocrine tissues. 42

CONCLUSION

The present study demonstrates that hypothyroidism and hypoparathyroidism are major health issues encountered by patients with beta-thalassemia major despite the standard medical therapies. Close monitoring, the timely institution of therapy, and aggressive nutritional support are essential variables to improve their outcome and general well-being.

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