Original Article

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The correlation of vitamin D3 with biochemical markers in β-Thalassemia major patients

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ABSTRACT

Background: Vitamin D3 is essential for pediatric development and normal growth. **Aim:** This study aims to analyze the hematological characteristics of both β-thalassemia patients and controls; their liver and renal functions; and calcium, phosphorus, and parathyroid hormone levels and their correlation with vitamin D3. **Methods:** Ninety teenage subjects, comprising 45 patients with β-thalassemia major (selected from the Hereditary Blood Diseases Center in Basrah during their regular checkups) and 45 apparently healthy individuals selected from relatives and friends, aged between 12 to 15 years (42.2% males and 57.8% females) were included in a 2023 case-control study at the Hereditary Blood Diseases Center. A gel tube with approximately 5 mL of blood was utilized for biochemical analyses, and a portion of the sample was transferred into a test tube for complete blood count testing. Liver and renal functions were evaluated by measuring the activities of aspartate transaminase (AST), alkaline phosphatase (ALP), alanine transaminase (ALT), blood urea, and serum creatinine. Serum concentrations of parathyroid hormone, vitamin D3, calcium, and phosphorus were also estimated. Serum ferritin and complete blood count were performed as well. The Statistical Package for the Special Science version 29 was utilized, employing several methods to assess the connection between the variables, including the Mann-Whitney U test, Pearson Chi-Square, Pearson correlation, and linear regression (to assess the correlation between the variables). A p-value of < 0.05 was considered statistically significant. **Results:** Regarding demographics, the only significant difference was in BMI ($p = 0.0001$). ALT, AST, and ALP levels were significantly higher in β-thalassemia patients compared to healthy individuals, with significant differences ($p = 0.0001$ for all). Blood urea and serum creatinine levels were statistically significant ($p = 0.0001$). A highly significant difference was found in serum levels of vitamin D3 ($p = 0.0001$), with PTH significantly higher in patients ($p = 0.0001$). Calcium levels were also significantly different ($p = 0.0001$), but no significant difference was found in phosphorus levels ($p > 0.05$). Regarding hematological indices, a highly significant association was found in Hb, RBC, HCT ($p = 0.0001$), and MCV ($p = 0.025$) levels, while MCH, MCHC, WBCs, and platelets did not have significant differences ($p > 0.05$). **Conclusion:** β-Thalassemia significantly affects hematological and biochemical markers in all patients. Vitamin D3 levels are negatively correlated with ALT, AST, serum ferritin, PTH, and calcium levels in patients.

Keywords: Vitamin D3, β-thalassemia major, biochemical markers, BMI, hemoglobinopathy.

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INTRODUCTION

Hereditary disorders are among the most common disorders in humans.[1] The most prevalent of these is thalassemia, a group of inherited illnesses characterized by absent or minimal globin chain production. [2]

Thalassemia has garnered significant attention from the international public health community due to its effects on increased mortality and morbidity among affected individuals.[3] Genetic alterations in or near the globin

genes lead to abnormal α or β globin synthesis (the α- and β-thalassemia syndromes, respectively) or structural changes in hemoglobin such as sickle cell disease.[4]

Deficient generation of β globin chains results in a relative excess of α globin chains, causing β-thalassemia. Many clinical symptoms arise from these excess α globin chains, as they are insoluble and precipitate within red blood cells. Consequently, patients homozygous for defective β globin synthesis experience severe symptoms, while heterozygotes may have mild anemia without symptoms.[5]

Gene mutations resulting in low amounts and/or dysfunctional α and β globin proteins are clustered on chromosomes 16 and 11, respectively; in some cases, one of these proteins may be entirely absent.[6]

ß-thalassemia can be classified as thalassemia major (TM) or thalassemia intermedia (TI), depending on the severity of symptoms.[7]

In thalassemic patients, symptoms of vitamin D insufficiency are sometimes misdiagnosed as anemia or as side effects of chelation therapy, including back pain, joint discomfort, muscle weakness, and osteopenia/osteoporosis.[8] However, vitamin D supplementation has been shown to alleviate joint and back pain and improve tolerance for walking and other physical activities among thalassemic youth.[9]

The recommended threshold values for defining vitamin D status based on circulating levels, as estimated by Saggese et al,[10] are extreme deficit (less than 10 ng/mL), deficiency (<20 ng/mL), insufficiency (20–29 ng/mL), and sufficiency (≥ 30 ng/mL).

Accordingly, this study aims to estimate the relationship between vitamin D levels and biochemical markers among patients with β-thalassemia major in Basrah.

MATERIALS AND METHODS

Study design

A case-control study was conducted at Basrah Hereditary Blood Diseases Center from November 2023 to May 2024. Ninety pediatric subjects, consisting of patients with β-thalassemia major (case group) and 45 apparently healthy individuals (control group), of both genders, aged between 12 and 15 years, were included.

Biochemical and hematological investigations were performed for all study subjects, including complete blood count (CBC), blood urea, serum creatinine, AST, ALT, ALP, vitamin D3, PTH, serum ferritin, serum calcium, and phosphorus.

Study procedures

Board-certified gastroenterologists, who had dedicated, hands-on colonoscopic instruction as part of their fellowship training in gastroenterology, performed the procedures. Endoscopists used adult or pediatric variable-stiffness video colonoscopies.

We used the endoscopic evaluation of lesion detection. Patients were on a fluid diet 48 hours before the procedure and given 45 mL of 1:1 diluted sodium phosphate (Fleet Phospho-soda) orally at 22:00 the day before and 06:00 the day of the procedure. Bowel cleansing was integrated with a sodium phosphate enema, which was applied on the morning of the colonoscopy. Subsequently, 1 mg to 5 mg midazolam was given during sedation, and 20 mg to 50 mg Hyoscine-N-butyl bromide (scopolamine butyl bromide) IV was preferred as a spasmolytic. The investigations were executed using a Fujinon colonoscopy device.

Inclusion and exclusion criteria for patients

Patients with β-thalassemia major aged between 12 and 15 years were included in this study. Patients were excluded if they met the following criteria: thalassemia major patients aged less than 12 years or more than 15 years, patients with chronic diseases such as renal failure, liver diseases, and thyroid or parathyroid diseases, patients taking supplements affecting the results of biochemical tests (e.g., calcium), phosphorus (P) and vitamin D3), patients receiving hormone replacement therapy (HRT), such as growth hormone, and lastly patient with viral hepatitis.

Approval of ethical committee

The research proposal was approved by the ethics committee of the Faculty of Medicine at the University of Basrah.

Blood sample collection and preparation

Blood samples were collected from all participants, both cases and controls, by venipuncture using a disposable syringe while the participants were seated.

Approximately 5 mL of blood was drawn (an aliquot was used for hematological analysis), and the remaining sample was placed in gel tubes and allowed to clot for 1 to 2 hours at room temperature. The tubes were then put in the centrifuge for about 15 minutes at 2000 RPM for separation. After centrifugation, the supernatant (serum) was collected for assay. About 900 microliters (µL) of serum was divided equally into three small samples using a micropipette and placed in disposable small-sized tubes called Eppendorf or Polymerase Chain Reaction (PCR) tubes, changing the pipette tip between each sample. The samples were then stored in a deep freeze refrigerator (-20 to -30 ℃) for later use, avoiding repeated freezing and thawing.

Statistical analysis

The sample size was calculated based on the total number of β-thalassemia major patients aged between 12 and 15 years, using Steven K. Thompson's equation.
We utilized version 29 of the SPSS program to analyze the study's results. The Mann-Whitney U test was used to determine whether non-parametric quantitative data had statistically significant differences. Chi-square or Fisher's exact test was used to find statistically significant correlations between qualitative variables. The statistical significance of relationships between non-parametric quantitative data was assessed using Spearman's correlation test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Sociodemographic characteristics of the study subjects

Table (1) shows the age distribution into two groups: ages 12–13 years and ages 14–15 years. About 45.6% were in the 12–13 years group, and 54.4 % were in the 14–15 years group. Among the 90 participants, 42.2% were male and 57.8% were female. Among the patients, 37.8% were male and 62.2% were female, indicating a higher number of females in the patient group compared to 46.7% of males and 53.3% of females in the apparently healthy group. The table presents no significant statistical association regarding age and sex (p = 0.082, p = 0.393, respectively) in this study.

Overall, 73.3% of the β-thalassemia major patients had a BMI of <18.5 kg/m², 24.4% fell into the 18.5-24.9 kg/m² group, while 2.2 % belonged to the ≥ 25 kg/m² group. In the control group, 20% had a BMI of <18.5 kg/m², 64.4% fell into the 18.5-24.9 kg/m² group, and 15.5 % belonged to the ≥ 25 kg/m² group. A significant statistical association regarding BMI was found between the two groups (p = 0.0001).

When examining residency, it was found that 55.6% of study participants lived in the center of Basrah Governorate, while 44.4% lived in the periphery, without any significant statistical association (P=0.671) in it.

Regarding the distribution of blood groups, the most common blood group among both patients and controls was (A+) at 35.6%, while blood group (B-) was the least common at 2.2% in β-thalassemia major patients, with almost no one in the control group having blood group AB^+ or B-. As indicated in Table 1, no significant statistical association (p = 0.540) was noted between the blood group and being a thalassemia patient.

Table 1: Demographic characteristics of the study subjects (n = 90)

Characteristic Parameters		β TM (n = 45)	Control (n = 45)	Total No. (%)	p-value
Age (years)	(12-13)	22(48.8%)	19(42.2%)	41(45.6%)	0.082*
	(14-15)	23(51.1%)	26(57.8%)	49(54.4%)	
Sex	Male	17(37.8%)	21(46.7%)	38(42.2%)	0.393**
	Female	28(62.2%)	24(53.3%)	52(57.8%)	
BMI (kg/m²)	< 18.5	33(73.3%)	9(20%)	42(46.6%)	0.0001*
	18.5-24.9	11(24.4%)	29(64.4%)	40(44.4%)	
	≥ 25	1(2.2%)	7(15.5%)	8(8.8%)	
Residency	Center	26(57.8%)	24(53.3%)	50(55.6%)	0.671**
	Periphery	19(42.2%)	21(46.7%)	40(44.4%)	
Blood Group	A+	15(33.3%)	17(37.8%)	32(35.6%)	0.540*
	B+	11(24.4%)	15(33.3%)	26(28.9%)	
	AB+	2(4.4%)	0(0.0%)	2(2.2%)	
	O+	12(26.7%)	10(22.2%)	22(24.4%)	
	B-	1(2.2%)	0(0.0%)	1(1.1%)	
	O-	4(8.9%)	3(6.7%)	7(7.8%)	

*Fisher's Exact Test, ** Pearson Chi-Square
P-value < 0.05 is statistically significant.

Hematological parameters in β-thalassemia major patients and the control groups

Table 2 describes that Hb levels were notably higher in the control group, with a median value of 13 g/dL compared to 7.3 g/dL in TM patients. RBC counts were also higher in controls, with a median of 4.89×10^6/UL, while the median was 4.89×10^6/UL, and 2.7×10^6/UL in control and thalassemia patients respectively, and WBCs median was 6.8×10^3/UL, in both groups. After comparing blood parameters (i.e., Hb, RBC, WBCs, and platelets) between the patients and the control groups, the only significant statistical difference (p = 0.0001) observed was in Hb level and RBC count. Serum ferritin was significantly higher in patients (p = 0.0001), attributed to repeated blood transfusions.

Table 2: Differences in hematological parameters between thalassemia patients (n = 45) and controls (n = 45)

Parameter	Category	Mean ± SD	Median	Min	Max	Mean Rank	p-value*
Hb (g/dL)	β-TM	7.5 ± 0.81	7.3	6.1	10	23	0.0001
	Control	12.8 ± 1.1	13	10.2	15.2	68	
S. ferritin (ng/mL)	β-TM	2808.5 ± 1163.3	2722	699	5372	68	0.0001
	Control	34.1 ± 22.24	28	8	81	23	
RBC 10^6/UL	β-TM	2.82 ± 0.45	2.7	2.29	4.56	23.23	0.0001
	Control	4.83 ± 0.35	4.89	4.26	5.38	67.77	
HCT (%)	β-TM	21 ± 2.48	20.3	17	31	23.03	0.0001
	Control	37.5 ± 2.58	36.8	31.8	43.1	67.97	
MCV (FL)	β-TM	75.2 ± 5.56	75.4	59.7	82.8	39.37	0.025
	Control	77.73 ± 4.07	79	70	83	51.63	
MCH (Pg)	β-TM	26.3 ± 2.33	25.8	20.9	29.2	44.57	0.733
	Control	26.66 ± 1.78	27	22	29	46.43	
MCHC (g/L)	β-TM	35 ± 1.45	35.1	32.1	37	49.2	0.177
	Control	34.7 ± 1.68	34.4	32.1	39.8	41.8	
WBC (10^3/UL)	β-TM	11.93 ± 16.3	6.8	2.87	81.5	44.66	0.759
	Control	7.2 ± 1.46	6.8	4.4	10.5	46.34	
Platelets (10^3/UL)	β-TM	383 ± 280.8	311	100	1323	46.92	0.605
	Control	302 ± 74.5	275	190	465	44.08	

* Mann-Whitney U Test, βTM = βthalassemia major

Differences in biochemical parameters between thalassemia patients and controls

Table 3 displays that all markers, ALP, ALT, and AST levels, were significantly higher in patients (p = 0.0001 for all), indicating that β-thalassemia major significantly affects these markers.

Table 3: Differences in biochemical parameters (ALP, ALT, and AST) between thalassemia patients and controls

Parameter	Category	Mean ± SD	Median	Mean rank	p-value*
ALP (u/L)	β-TM	158.2 ± 86.2	125.00	62.21	0.0001
	Control	89.36 ± 8.87	90.00	28.79	
ALT (u/L)	β-TM	46.1 ± 36.4	34.00	63.1	0.0001
	Control	13.34 ± 8.1	11.00	27.9	
AST (u/L)	β-TM	44.6 ± 25.7	37.00	63.36	0.0001
	Control	19.5 ± 6.6	19.00	27.64	

* Mann-Whitney U Test; β-TM (n=45), Control (n=45)
p-value < 0.05 is statistically significant.

Differences in renal function test and ferritin between β-TM patients and control group

Table 4 lists that serum creatinine and blood urea levels were significantly different between cases and control groups (p = 0.0001 for both). The higher blood urea level in thalassemia patients may reflect compromised renal function, which could be exacerbated by iron overload and warrants further investigation.

Table 4: Differences in renal function test between β-thalassemia major patients and control group

Parameter	Category	Mean ± SD	Median	Mean Rank	P-value*
Creatinine (mg/dL)	β-TM	0.51 ± 0.24	0.45	34.71	0.0001
	Control	0.54 ± 0.09	0.52	56.29	
Blood Urea (mg/dL)	β-TM	25 ± 8.65	23.00	57.38	0.0001
	Control	17.8 ± 4.87	17.00	33.62	

* Mann-Whitney U Test; β-TM (n = 45), control (n = 45)

Differences of Vit. D3, PTH, calcium, and phosphorus between β-TM patients and control group

Table 5 shows that vitamin D3, PTH, and calcium levels were significantly different between patients and the control group (p = 0.0001 for all). Vitamin D3 levels were higher in the control group, while PTH levels were lower. Median serum calcium levels in both groups were approximately equal, reflecting a symmetrical distribution of the obtained data. Conversely, phosphorus levels were normal in study subjects and demonstrated no statistically significant difference (p = 0.475), with medians of 3.4 and 3.6 in the patients and control groups, respectively.

Table 5: Differences of (vitamin D3, PTH, calcium, and phosphorus) between thalassemia patients and control group

Parameter	Category	Mean ± SD	Median	Mean Rank	p-value*
Vitamin D3 (ng/mL)	β-TM	10.8 ± 4	9.45	23	0.0001
	Control	35.34 ± 2.4	35.3	68	
PTH (Pg/mL)	β-TM	161 ± 47	161	67.04	0.0001
	Control	16.65 ± 4.35	16.5	23.96	
Calcium (mg/dL)	β-TM	11.65 ± 0.7	11.6	58.48	0.0001
	Control	10.7 ± 0.95	11	32.51	
Phosphorus (mg/dL)	β-TM	3.5 ± 0.94	3.4	43.53	0.475
	Control	3.66 ± 1.07	3.6	47.47	

* Mann-Whitney U Test

Correlations of biochemical markers with vitamin D3 in study subjects

Table 6 details the correlation of ALP, ALT, and AST with vitamin D3 in both groups, where most markers were positively correlated with vitamin D3 while ALT and AST were negatively correlated in patients. All these correlations were statistically non-significant (p-value > 0.05), except for ALP, ALT, and AST in the control group, which were statistically significant (p-value < 0.05).

For the correlation of renal function tests and ferritin with vitamin D3 in both groups, a positive correlation was found between renal function tests and vitamin D3. Conversely, ferritin was negatively correlated in patients and positively correlated in the control group. However, these correlations were statistically non-significant (p-value > 0.05), except for ferritin in the control group (p = 0.029).

Finally, the correlation of PTH, calcium, and phosphorus with vitamin D3 in study subjects was assessed. PTH was negatively correlated with vitamin D3 in both groups, while calcium was negatively correlated in patients but positively correlated in the control group. Phosphorus was positively correlated in both groups, but none of the

correlations showed statistical significance (p-value > 0.05), except for calcium in patients (p-value < 0.05).

Table 6: Correlation between biochemical markers and vitamin D3 in β-TM patients and control group

Correlated parameter vs. vitamin D3	βTM (n = 45)		Control (n = 45)	
	R-value	p-value	R-value	p-value
ALP	0.164	0.282	0.369	0.013
ALT	-0.086	0.574	0.484	0.0001
AST	-0.047	0.759	0.546	0.0001
S. Creatinine	0.093	0.541	0.275	0.068
Blood urea	0.07	0.647	0.156	0.305
Serum ferritin	-0.22	0.144	0.325	0.029
PTH	-0.144	0.344	-0.016	0.916
Ca	-0.369	0.013	0.078	0.613
Phosphorus	0.054	0.727	0.271	0.072

*Spearman Correlation R: Correlation Coefficient

DISCUSSION

β-Thalassemia is a hereditary condition that causes iron overload and persistent anemia due to ineffective erythropoiesis.[11] Patients require frequent blood transfusions to prevent complications such as chronic anemia and alterations in bone structure, leading to iron overload in their systems.[12] Despite recent advancements in chelation therapy to reduce iron excess, the quality of patients' lives remains at risk due to endocrinopathies.[13] Additionally, a range of hematological and biochemical anomalies constitutes further symptoms in these patients.[14] The current investigation examined the hematological and biochemical variables among a sample of patients with β-thalassemia major and compared them with a control group in a case-control study.

Table 1 reveals that there was no statistically significant association between the two groups in age, sex, residence, and blood groups, except BMI, and this finding was consistent with a previous study by Ali Akbar Asadi et al.[15] This may be attributed to undernutrition, basal metabolic rate profiles, trace mineral deficiencies, susceptibility to infections, oxidative stress, chronic anemia, psychosocial status, and various endocrinopathies such as hypogonadism and hypothyroidism.[16-18]

A reduced oxygen-carrying capacity results from the deficiency of all beta-globin chains in β-TM, impacting the synthesis of Hb within red blood cells. Microcytic hypochromic anemia and low RBC MCV are the outcomes of this condition, aligning with findings by Khawaji et al.[19] Noticeably, serum ferritin was significantly higher in patients (median = 2722 ng/mL), attributed to improper chelation therapy and chronic blood transfusions, which is consistent with Sura Zahim Hussein's findings. [20]

Liver enzyme levels were higher in patients, as seen in Table 3, indicating potential liver dysfunction, chronic viral hepatitis, iron overload, or vitamin D3 deficiency, which exacerbate liver dysfunction due to its role in calcium homeostasis and muscle health. These results are consistent with earlier research.[21]

On the other hand, blood urea and serum creatinine levels were statistically significantly different between thalassemia patients and the control group, as presented in Table 4. This finding is similar to that of Mahmoud et al[22] but disagrees with Şen et al.[23]

Regarding PTH, levels were significantly higher in thalassemia patients, as explained in Table 5, usually due to iron overload. This study aligns with findings by Meropi Dimitriadou A et al.[24]

In the current study, the mean serum vitamin D3 levels in thalassemic patients were considerably lower than in controls, with a significant correlation between bone disease and thalassemia-related vitamin D3 deficiency and insufficiency. This result is consistent with Ashraf Soliman V et al. [25]

Calcium levels were slightly higher in patients than in controls, opposing previous studies by Shamshiraz et al. (26), but the difference was significant. Phosphorus levels were normal in both groups and insignificant, which aligns with findings by a related study.[27] Other research has indicated that thalassemic patients had considerably higher serum phosphorus levels than control groups.[28]

Regarding the correlation between biochemical markers and vitamin D3, as outlined in Table 6, there was a negative and non-significant correlation between ALT, AST, ferritin, as well as calcium, and vitamin D3 in

patients. PTH was negatively correlated in both patient and control groups. Additionally, these correlations (ALP, AST, ALT, and ferritin) were positively and significantly different in the control group ($p < 0.05$), contradicting the findings by Abdelmotaleb G et al.[29]

CONCLUSIONS

Among children with β-thalassemia major, hematological and biochemical parameters were significantly affected. Vitamin D3 deficiency was prevalent, and low BMI was observed. These anomalies require frequent monitoring for early identification and treatment, as they may result from iron overload and inadequate nutritional support.

Limitations and recommendations

Given the high prevalence of vitamin D3 deficiency in thalassemia patients, routine screening and supplementation should be considered. Future research should focus on longitudinal studies to better understand the causality between vitamin D3 levels and biochemical abnormalities.

The main limitations relate to sampling, the stability, and the cost of markers, especially in private laboratories.

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