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Evaluation of Vitamin D level in thalassemia patients: The experience of a single center

Alaa M. Al-Rubae, Ahmed I. Ansaf, Safa A. Faraj

Abstract:

BACKGROUND: Beta-thalassemia, a hereditary blood disease transmitted through families, has become increasingly relevant with rising life expectancies, leading to bone disease being a significant cause of morbidity. Among the symptoms observed in these patients, bone pain and back pain are frequently reported. Vitamin D is believed to play a crucial role in reducing these symptoms.

AIM: The objective of this study was to assess the Vitamin D levels in thalassemic patients and investigate potential correlations with other factors.

PATIENTS AND METHODS: A cross-sectional study was conducted, involving a random selection of 48 patients with beta-thalassemia (major and intermediate types) aged 7 years and above. The patients were registered at the Hereditary Blood Disease Center in Wasit province, located in the South of Iraq, during the period from January to May 2022. Demographic data, including age, sex, address, diagnosis, type of chelation therapy, and frequency of blood transfusions, were collected from patients' files. Biochemical data, such as mean hemoglobin, mean serum ferritin, mean serum calcium, and Vitamin D levels at the time of the study, were also recorded. Vitamin D levels below 30 ng/ml were considered low level or deficiency, whereas 30 ng/ml and above were considered normal, as indicated by the kit manufacturer. Furthermore, the height, weight, and body mass index were evaluated in the studied patients with their written consent. SPSS version (23) was employed for data management and statistical analysis, utilizing a significant $P = 0.05$ and the Pearson's correlation.

RESULTS: The study revealed that 42 patients (87.5%) had low Vitamin D levels (below 30 ng/ml). The mean Vitamin D level was 18.23 ng/ml, with a maximum reading of 45 ng/ml. It was observed that Vitamin D deficiency was more prevalent in younger patients and those with higher ferritin levels, although the differences were not statistically significant.

CONCLUSION: Vitamin D deficiency is common in patients with B-thalassemia, as indicated by this study.

Keywords:

Serum ferritin, thalassemia, Vitamin D

Introduction

Beta-thalassemia is the most common hereditary blood disease in Iraq.[1]

With improvement in iron chelation therapy by the use of oral deferasirox, the life span is increased but with possible multisystemic complications.[1] Bone disease and its related symptoms can cause important morbidity for thalassemia patients and affect the quality of their life.[2]

Symptoms of Vitamin D deficiency in thalassemic patients are frequently confused with anemia and chelation therapy side effects such as joint and back pain, muscle weakness, and osteopenia/osteoporosis.[3] However, medication with Vitamin D has been found to relieve back and joint problems, as well as greater

Department of Pediatrics, College of Medicine, Wasit University, Kut, Iraq

Address for correspondence:
Dr. Safa A. Faraj, Department of Pediatrics, College of Medicine, Wasit University, Kut, Iraq.
E-mail: safaafaraj@uowasit.edu.iq

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tolerance for walking and activity in thalassemic teenagers.[4]

The aim of this study is to evaluate Vitamin D level as a hidden or unrecognized deficiency and its related factors.

Patients and Methods

This is a cross-sectional study done on randomly selected 48 patients with beta-thalassemia (major and intermediate) registered at the Hereditary Blood Disease Center, which include more than 450 registered patients with different inherited blood diseases at Wasit province in the South of Iraq. This study was done from January to May 24, 2022. Written consent was obtained from the selected patients. One kit for Vitamin D measurement contain fifty samples were used in the study, two patients who having aplastic anemia were excluded from the study. This study was approved by review ethical committee of Wasit hereditary blood diseases center.

This test is not routinely available in the hereditary blood disease Center.

The age for the included patients was 7 years and above.

Demographic data were collected from patient's files, including age, sex, address, diagnosis, type of chelating treatment deferasirox or deferoxamine, presence complications (such as, diabetes mellitus [DM], hypothyroidism, cardiomyopathy, and hepatitis C and B infection), and the frequency of blood transfusion.

The biochemical and hematological investigations were done in the laboratory of hematology center including the mean hemoglobin (Hb), the mean serum ferritin level, mean calcium level, and Vitamin D3 level by MINI VIDAS immunoassay.

The height, weight, and body mass index (BMI) were measured at the center at the time of the study.

IBM SPSS-23 (IBM Statistical Packages for the Social Sciences, version 29, Chicago, Illinois, United States). was used for the data management, and statistical analytic was used to determine the frequency with a significant $P = 0.05$ and Pearson's correlation.

Results

In this study, a total of 34 patients (70.8%) were diagnosed with thalassemia major, whereas 14 patients (29.2%) had thalassemia intermediate, and two were found to have sickle thalassemia. Out of the patients, 23 (47.9%) were male and 25 (52.1%) were female [Table 1].

Table 1: Demographic data of the patients

Item	*n* (%)
Ages of patients/years*, range	7–58 (25.7; 1.2)
BMI*, range	14–32 (20.9; 4.1)
Diagnosis	
β-thalassemia major	34 (70.8)
β-thalassemia intermediate	14 (29.2)
Gender	
Males	23 (47.9)
Females	25 (52.1)
Iron chelation	
Deferasirox	31 (64.6)
Deferoxamine	13 (27.1)
No treatment	4 (8.3)
Blood transfusion	
Every 2 weeks	35 (72.9)
Every 3–4 weeks	8 (16.7)
Every 2–3 months	5 (10.4)
Complication	
Hypothyroidism	3 (6.3)
DM	3 (6.3)
Cardiomyopathy	2 (4.2)
Hypothyroidism and heart failure	1 (2.1)
Hepatitis C	18 (37.5)

*Mean and SD. SD=Standard deviation, BMI=Body mass index, DM=Diabetes mellitus

Regarding chelation therapy, 31 patients (64.6%) were administered deferasirox, 13 patients (27.1%) were given deferoxamine, and four patients (8.3%) did not receive any chelating drug.

The frequency of blood transfusions varied among the patients. Thirty-five patients (72.9%) received blood transfusions every 2 weeks, eight patients (16.7%) received them every 3–4 weeks, and five patients (10.4%) had blood transfusions every 2–3 months.

The complications were also recorded in the studied patients. Hypothyroidism and DM were found in three patients (6.3%), cardiomyopathy in two patients (4.2%), and one patient (2.1%) had both hypothyroidism and heart failure. In addition, hepatitis C infection was reported in 18 patients (37.5%) [Table 1].

Serum ferritin levels were analyzed, revealing that 11 patients (22.9%) had levels below 1000 ng/dl, 15 patients (31.3%) had levels between 1000 and 3000 ng/dl, and 21 patients (43.8%) had serum ferritin levels exceeding 3000 ng/dl [Table 1].

The participants' age ranged from 7 to 58 years, with an average age of 25.7 years. The Vitamin D levels ranged from 8 to 45 ng/ml, with a mean of 18.23 ng/ml. Serum ferritin levels varied between 200 ng/dl (minimum) and 12,000 ng/dl (maximum), with a mean of 3359 ng/dl. The average Hb (Hb) level was 8.7 g/dl and the mean BMI was 20.9, as shown in Table 2.

The patients in the study were categorized based on their Vitamin D levels, with levels less than 30 ng/ml considered low (or deficient) and levels ≥30 ng/ml considered normal, as specified by the kit manufacturer. Among the patients, 42 (87.5%) had low Vitamin D levels (<30 ng/ml), whereas 6 patients (12.5%) had 30 ng/ml or higher, as depicted in Table 2.

The correlation between Vitamin D levels and patients' ages was examined. For patients aged 7–15 years, the mean Vitamin D level was 15.27 ng/ml. In the age group of 16–25 years, the mean Vitamin D level was 17.53 ng/ml, and for older patients, above 25 years, the mean Vitamin D level was 20.31 ng/ml, with $P = 0.2$, as shown in Table 3.

The study examined the correlation between Vitamin D and serum ferritin levels. For patients with serum ferritin levels below 1000 ng/dl, the mean Vitamin D level was 19.91 ng/ml. Among those with serum ferritin levels ranging from 1000 to 3000 ng/dl, the mean Vitamin D level was 17.17 ng/ml. Patients with serum ferritin levels exceeding 3000 ng/dl had a mean Vitamin D level of 18.22 ng/ml, and *P* value for this correlation was found to be 0.7, as presented in Table 3.

Table 2: Selected hematological and biochemical data for the studied patients

Item	*n*	Minimum	Maximum	Mean	SD
Vitamin D level (ng/mL)	48	8	45	18.23	8.5
Serum ferritin level (ng/dL)	47	200	12,000	3359.47	2.9
Hb (g/dL)	48	7	15	8.72	1.1
Serum calcium (mg/dL)	48	5	10	8.79	1.076
Vitamin D level, *n* (%)					
<30 ng/mL			42 (87.5)		
30 ng/mL and more			6 (12.5)		

SD=Standard deviation, Hb=Hemoglobin

Table 3: Correlation between Vitamin D level and other variables

Item	*n*	Vitamin D (mean ng/mL)	SD	Range	*P*
Age group/years					
1–15	11	15.27	5.1	8–24	0.2
16–25	16	17.53	7.9	8–37	
>25	21	20.31	10.1	8–45	
Serum ferritin (ng/dL)					
<1000	11	19.91	11.0	8–45	0.7
1000–3000	15	17.16	7.6	8–36	
>3000	21	18.22	8.2	8–37	
Total	47	18.28	8.6	8	
Iron chelation					
X-jade	31	17.20	8.2	8–37	0.1
Desferal	13	18.23	7.2	8–32	
No treatment	4	26.25	12.8	18–45	
Total	48	18.23	8.5	8–45	

SD=Standard deviation

Furthermore, the correlation between the type of iron chelator used and Vitamin D levels was evaluated. Among the 31 patients receiving chelation treatment, those using oral chelating deferasirox had a mean Vitamin D level of 17.20 ng/ml, whereas those using parenteral deferoxamine had a mean Vitamin D level of 18.23 ng/ml.

Interestingly, four patients who did not undergo chelation therapy had a higher mean Vitamin D level of 26.25 ng/ml. However, this difference was not statistically significant ($P = 0.1$), possibly due to the small number of patients not taking chelation therapy in this study. This information is summarized in Table 3.

In scatter Figure 1, the Pearson's correlation between the age of the studied patients and Vitamin D level was positive (Pearson's value = 0.14, $P = 0.3$).

In scatter Figure 2, the correlation between ferritin level and Vitamin D was negative (Pearson's value −0.02, r −0.02).

Discussion

In everyday medical practice, it is quite common to encounter patients with beta-thalassemia who frequently report symptoms such as back pain, neck pain, leg pain, and knee pain, which significantly impact their daily activities such as attending school, playing with peers, and engaging in routine life activities. There can be various underlying causes responsible for these symptoms. However, one important aspect that often goes unnoticed and undertreated in thalassemic patients is the evaluation of their Vitamin D levels. This oversight may occur because the mentioned manifestations can

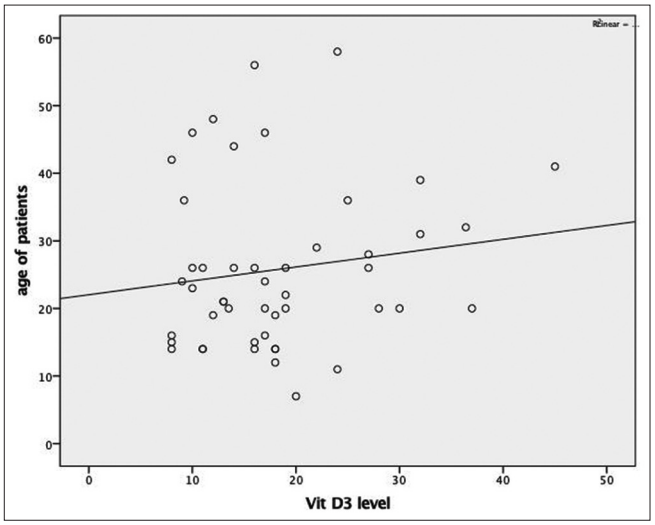

Figure 1: Linear correlation between the age and Vitamin D level

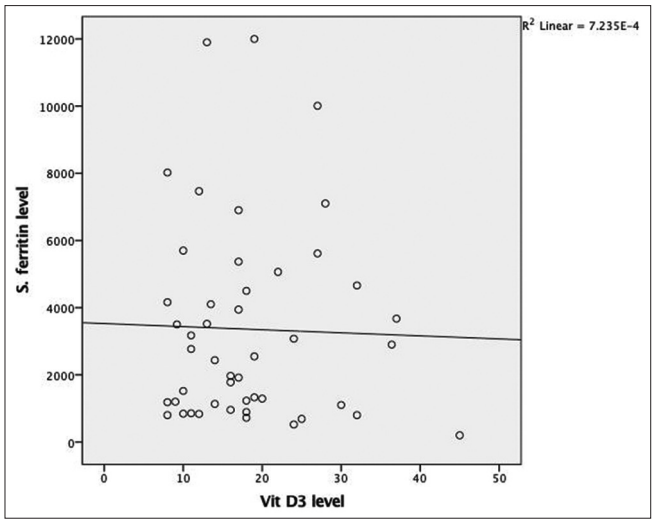

Figure 2: Linear correlation between serum ferritin and Vitamin D level

be easily misinterpreted as typical consequences of conditions such as extramedullary hematopoiesis, effects of iron overload, or side effects of chelation therapy. Hence, the importance of assessing and managing Vitamin D levels in these patients might be overlooked, potentially contributing to the persistence of their symptoms.[5,6]

In this study, it was observed that 87.5% of the β-thalassemia patients had low Vitamin D levels, with a mean of 18.23 ng/ml. These findings are consistent with other studies conducted in different regions. For instance, a study by Dhale *et al*. in India reported that 77.7% of thalassemia patients had low Vitamin D levels, with a mean of 16.26 ng/ml.[5] Similarly, Fahim *et al*.'s study in Egypt found that 91% of the studied patients had Vitamin D insufficiency or deficiency.[6] Vogiatzi *et al*.'s study in North America reported that 81.8% of the patients had insufficient or inadequate Vitamin D levels.[7]

Various factors have been proposed to explain the low Vitamin D levels in thalassemia patients. One common explanation is hepatic dysfunction, which can lead to defective hydroxylation of Vitamin D, resulting in decreased serum levels.[5,6,8,9] Some studies have also suggested the involvement of endocrine hypofunction, such as hypoparathyroidism, which impacts bone metabolism and may lead to a combination of hypovitaminosis D and hypoparathyroidism.[10-12] Lower parathyroid hormone (PTH) levels have been found in multitransfused thalassemia patients, suggesting that these patients could benefit from Vitamin D and calcium therapy.[13,14]

Unfortunately, in this study, testing PTH levels to confirm the relation was not feasible due to its unavailability in the center and its high cost in the private facilities. Other potential contributing factors to low Vitamin D levels include dietary factors such as low intake of vegetables and high consumption of carbonated soft drinks, as well as poor compliance with Vitamin D supplementation.

In addition, thalassemic patients are at a higher risk of Vitamin D deficiency due to reduced sun exposure and decreased bone mass.[5,15] High serum ferritin levels have been suggested to correlate with low Vitamin D levels, possibly due to calcium metabolism impairment, and the upregulated absorption of iron, which reduces calcium absorption.[16-18] Furthermore, high ferritin levels may interfere with 25-hydroxyvitamin-D production in the liver due to hepatic iron overload and negatively affect bone metabolism.[19,20] However, in this study, the statistical analysis did not yield a significant *P* value to confirm this correlation.

Conclusion

Vitamin D deficiency is common in patients with β-thalassemia disease as direct or indirect effects of this chronic multisystem disorder.

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Conflicts of interest
There are no conflicts of interest.

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