Journal of
Kerman University of Medical Sciences

https://jkmu.kmu.ac.ir
10.34172/jkmu.2024.05
Vol. 31, No. 1, 2024, 29-34

Original Article

Open Access
Publish Free

Vitamin D and Calcium Deficiency and its Relationship with Cardiac Function in Patients with Beta-Thalassemia

Maryam Ahmadipour[1], Ahamd Naghibzadeh-Tahami[2], Koroush Mirzaie[3], Elham Maleki[1*]

[1]Department of Pediatrics, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[2]Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
[3]Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

***Corresponding Author:** Elham Maleki, Email: pediatric18811@yahoo.com

Abstract

Background: Heart disease is the leading cause of mortality and morbidity in patients with beta-thalassemia. Vitamin D and calcium deficiency are common in these patients. We studied and compared vitamin D and calcium levels and other parameters with echocardiographic findings in patients with beta-thalassemia.

Methods: A cross-sectional study on patients with transfusion-dependent thalassemia was conducted. One hundred sixty-nine patients with transfusion-dependent thalassemia were enrolled. Ejection fraction, valvular insufficiency, and aortic diameter were determined. The aortic diameter of patients was measured using the Mindray DC60 echo model. All of these patients were tested for levels of vitamin D, calcium (Ca), parathyroid hormone (PTH), alkaline phosphatase (ALP), platelet (PLT), and ferritin. Finally, the effect of these factors on aortic root (AR), aortic valve area (AVA), and ejection fraction (EF) was evaluated. One-way ANOVA was used to compare quantitative variables, and a chi-square test with a 95% confidence level was used to estimate relationships and compare ratios in groups.

Results: A statistically significant relationship existed between vitamin D deficiency and serum Ca (P value = 0.009). Our results showed that EF also increased with the increase in vitamin D levels, and the probability that the AR would have a normal size increased. Furthermore, abnormal PTH and PLT levels caused a decrease in EF.

Conclusion: This study showed an association between vitamin D deficiency and cardiac function in patients with transfusion-dependent thalassemia. Vitamin D can be considered a supplement for thalassemia patients.

Keywords: Beta-thalassemia, Vitamin D levels, Cardiac function, Aortic root, Aortic valve area, Ejection fraction

Citation: Ahmadipour M, Naghibzadeh-Tahami A, Mirzaie K, Maleki E. Vitamin D and calcium deficiency and its relationship with cardiac function in patients with beta-thalassemia. *Journal of Kerman University of Medical Sciences*. 2024;31(1):29–34. doi: 10.34172/jkmu.2024.05

Received: September 30, 2023, **Accepted**: December 17, 2023, **ePublished**: February 29, 2024

Introduction

Thalassemia, caused by a disruption in the synthesis of the protein part of the hemoglobin molecule, is one of the common genetic diseases in Iran. As a result, the oxygen supply to the organs is disturbed (1). Thalassemia has two main types, alpha and beta, based on the defect or non-production of globin chains. Each of these two types has several sub-branches (2).

Thalassemia is more common in the Mediterranean basin, tropical areas, and areas close to them in Asia and Africa; parts of Africa, Turkey, Iran, India, and Southeast Asia are called the global thalassemia belt (3). Iran is also located on this belt, and compared to other countries in this area, it has a high incidence rate of beta-thalassemia (4).

Furthermore, the average prevalence rate of thalassemia carriers in Iran is 4%, varying in different provinces, with the highest prevalence rate of 9.5% in Kerman (5). Clinical symptoms of beta-thalassemia major usually appear between 6 and 24 months of age. They are caused by the continuous destruction of defective red blood cells, which is why these patients need lifelong blood transfusions to survive. Despite the administration of iron chelators such as deferoxamine (alongside blood transfusion), all these patients have some degree of iron overload due to the recycling of iron resulting from the destruction of red blood cells. Iron deposition in the body's vital organs, including the cardiovascular system, will cause heart failure (6,7). Research has shown that more than half of the deaths in thalassemia patients are caused by this complication (8). According to recent studies, heart complications in thalassemia patients can be influenced by other factors, such as the balance of vitamin D and calcium (Ca) (9,10).

On the other hand, damage to the parathyroid gland in these patients (due to iron accumulation) will lead to disturbances in Ca metabolism, and the result of these extensive changes will be a negative impact on vitamin D and Ca levels (11,12). In several studies, vitamin D

deficiency has been reported in thalassemia patients (13), and in a case-control study, it was shown that 82% of people with thalassemia have vitamin D deficiency. In addition, some studies have observed a direct relationship between vitamin D deficiency and heart function (14). Despite the mentioned reasons, the information obtained in this field still needs to be revised. A relationship between vitamin D deficiency and iron levels or cardiac function has not been observed in patients with transfusion-dependent thalassemia (15).

Therefore, to detect the criteria of aortic involvement, valve size, sinotubular junction, and the initial part of the ascending aorta were compared with normal values.

The prevention of heart disease plays a vital role in increasing life expectancy and improving the quality of life of these patients. The studies on the relationship between vitamin D levels and cardiovascular diseases in these patients are limited and have yielded conflicting results. This issue reduces the generalizability of the results of these studies. Therefore, the present study was designed to investigate the relationship between vitamin D levels and heart function in patients with beta-thalassemia to investigate newer aspects of factors affecting cardiac complications in these patients.

Materials and Methods

The current study was a cross-sectional study conducted between 2018 and 2019 in Kerman city. The statistical population of this study was patients with thalassemia in Kerman. Based on this, 169 people were included in the study using the available sampling method. The inclusion criterion was thalassemia major. Also, patients who, besides thalassemia, had cardiovascular complications caused by concomitant diseases such as Marfan syndrome were excluded from the study.

Data collection

Using the Mindray DC60 echo model, the ventricular function (ejection fraction), valvular insufficiency, and aortic diameter of patients were measured, and the obtained values were compared with normal values based on the body surface, age, and gender of the people, and normal and abnormal values were interpreted. A 25(OH) vitamin D ELISA kit was used to evaluate the vitamin level.

Ferritin, Ca, parathyroid hormone (PTH), platelet (PLT), and alkaline phosphatase (ALP) levels were also extracted from the records during six months, and patients were classified into two groups, normal and abnormal, based on the status of ferritin, Ca, ALP, PTH, and PLT. Based on blood vitamin D levels, they were divided into three groups: deficient, insufficient, and sufficient.

Aorta size is strongly related to body surface area (BSA) and age. Therefore, BSA predicts aortic root (AR) diameter in several age intervals. Ozdemir and et al age-based classification is used to evaluate the echo criteria (16). They used published equations to consider three age strata: younger than 20 years, 20–40 years, and older than 40 years. These normal values have been accepted to date as the reference values. Aortic root dilatation at the sinuses of Valsalva is defined as an AR diameter above the upper limit of the 95% confidence interval (CI) of the distribution in a large reference population. In adults, a 2.1 cm/m^2 diameter has been considered the upper normal range in the ascending aorta.

Also, the demographic variables of age, sex, and place of residence were recorded in the data collection checklist. The relationship between the level of ferritin, vitamin D, Ca, ALT, PTH, and PLT and the diameter of the aorta and cardiac output was assessed. One-way ANOVA was used to compare quantitative variables, and a chi-square test with a 95% confidence level was used to estimate relationships and compare ratios in groups. All analyses were performed using Stata 17 software (Stata Corp., College Station, TX, USA).

Results

The main characteristics of the patients and the laboratory findings are shown in Table 1. A total of 169 patients (50.60% male and 49.40% female) with transfusion-dependent thalassemia participated in the study. Of the patients, 40% lived in the suburbs and 60% in the city. All patients were receiving iron chelation therapy. The overall mean age of the patients was 22.94 ± 8.57. In the group with vitamin D deficiency, 40% were women and 60% were men, and in the group with sufficient vitamin D, 61% were men and 30% were women. The two sexes had a borderline statistically significant difference in vitamin D levels ($P = 0.05$).

Patients with vitamin D deficiency had significantly higher ferritin levels (3708.01 ± 2407.72) compared to those with insufficient (2735.21 ± 2422.15) and sufficient (1904.06 ± 1715.28) vitamin D levels ($P = 0.0001$).

Also, the overall mean Ca level was 9.0 ± 0.55, and the highest level was 9.13 ± 0.48 in the sufficient vitamin D group. There was a statistically significant difference between the three vitamin D levels based on their Ca levels ($P = 0.0009$). Other findings are shown in Table 1.

Table 2 shows the results of the relationship between ejection fraction (EF) and factors affecting it. As can be seen, 50% of patients with normal ferritin had abnormal EF. This value was 51.5% for patients who had abnormal ferritin, and this difference was not statistically significant, i.e., ferritin had no effect on heart function in these patients ($P = 1$).

Among patients with sufficient vitamin D, about 42%, and among those with insufficient vitamin D, about 43% had normal EF. Among vitamin D-deficient subjects, about 57% of patients had normal EF, which shows that with the increase in vitamin D, the EF also increased.

Table 1. Main characteristics and laboratory parameters of patients with transfusion-dependent thalassemia grouped by vitamin D status

Variable	Total (N = 169)	Vitamin D sufficiency (30–100 ng/mL, sufficient)	Vitamin D insufficiency (20–30 ng/mL, insufficient)	Vitamin D deficiency (< 20 ng/mL deficient)	*P* value
Age (years), mean ± SD	22.94 ± 8.57	21.92 ± 10.51	22.58 ± 7.31	24.15 ± 7.07	0.3
Gender, No. (%)					0.05
Male	85 (50.60)	34 (60.71(	26 (54.17(	25 (39.06)	
Female	83 (49.40)	22 (39.29)	22 (45.83)	39 (60.94)	
Ferritin (ng/mL), mean ± SD	2828.75 ± 2322.20	1904.06 ± 1715.28	2735.21 ± 2422.15	3708.01 ± 2407.72	0.0001
Ca (mg/dL), mean ± SD	9.0 ± 0.55	9.13 ± 0.48	9.07 ± 0.50	8.84 ± 0.61	0.009
ALP (IU/L), mean ± SD	358.91 ± 199.49	400.04 ± 191.97	329.82 ± 169.34	344.74 ± 222.66	0.15
PTH (pg/mL), mean ± SD	26.73 ± 32.31	24.06 ± 32.31	24.01 ± 10.34	31.18 ± 20.60	0.16
PLT 1000/cumm, mean ± SD	399.52 ± 197.77	411.98 ± 178.89	412.26 ± 211.02	382.22 ± 213.49	0.64
AVA, mean ± SD	22.34 ± 3.70	22.26 ± 4.36	22.60 ± 3.02	22.22 ± 3.54	0.85
AR, mean ± SD	31.24 ± 6.41	31.91 ± 8.86	31.48 ± 3.59	30.49 ± 5.46	0.46

Abbreviations: Ca, calcium; ALP, alkaline phosphatase; PTH, parathyroid hormone: PLT, platelet; AVA, aortic valve area; AR, aortic root.

Table 2. The relationship between the levels of ferritin, Ca, ALP, PTH, PLT, and vitamin D with EF

Variable	EF		*P* value
	Normal (> 60), No. (%)	Abnormal (< 60), No. (%)	
Ferritin			
Normal (24–124 mg/dL)	1 (50)	1 (50)	1
Abnormal (< 24, > 124 mg/dL)	81 (48.5)	86 (51.5)	
Ca			
Normal (8.2–10.5 mg/dL)	78 (48.4)	83 (51.6)	1
Abnormal (< 8.2, > 10.5 mg/dL)	4 (50)	4 (50)	
ALP			
Normal (180–1200 IU/L)	72 (48.6)	76 (51.4)	1
Abnormal (< 180, > 1200 IU/L)	10 (47.6)	11 (52.4)	
PTH			
Normal (8–76 pg/mL)	78 (49.4)	80 (50.6)	0.53
Abnormal (< 8, > 76 pg/mL)	4 (36.4)	7 (63.6)	
PLT			
Normal (150–450)	52 (46.4)	60 (53.6)	0.51
Abnormal (< 150, > 450)	30 (52.6)	27 (47.4)	
Vitamin D_3			
< 20 ng/mL Deficient	37 (57.8)	27 (42.4)	0.18
20–30 ng/mL Insufficient	21 (43.8)	27 (56.3)	
31–100 ng/mL Sufficient	24 (42.9)	32 (57.1)	

Abbreviations: EF, ejection fraction; Ca, calcium; ALP, alkaline phosphatase; PTH, parathyroid hormone; PLT, platelet.

However, this relationship was not significant ($P = 0.18$). Furthermore, 50.6% of patients with normal PTH levels had abnormal EF, even though this value was 63.6% for patients with abnormal PTH levels, which indicates that disorder in PTH levels causes a decrease in EF. The relationship is not significant here either ($P = 0.53$).

Although the observed relationship between PLT levels and EF is insignificant ($P = 0.51$), the results indicate that EF decreases in these patients with a disordered level of blood PLT, i.e., normal EF was seen in 53.6% of patients with abnormal platelets, but 47.4% had abnormal EF.

Table 3 shows the effect of ferritin, Ca, ALP, PTH, PLT, and vitamin D levels on the aortic valve area (AVA). 72.4% of patients with abnormal ferritin had abnormal AVA, and this difference was borderline significant ($P = 0.06$).

In patients with abnormal Ca levels, 92% had abnormal AVA although in those whose Ca was within the normal range, only 70.6% had abnormal AVA. This difference was close to the significant level ($P = 0.08$)

In patients who had abnormal ALP, 84% had abnormal AVA, but in patients whose ALP was in the normal range, only 70% had abnormal AVA ($P = 0.13$). However, this frequency difference implies that ALP outside the normal range increases the probability of abnormal AVA.

Furthermore, 75% of patients with vitamin D deficiency, 67.2% with insufficient vitamin D, and 70.5% with normal vitamin D levels had abnormal AVA, which shows that increasing the vitamin D level decreases the probability of abnormal AVA. The differences between these three groups were not statistically significant ($P = 0.18$).

Table 4 shows the effect of ferritin, Ca, ALP, PTH, PLT, and vitamin D levels on AR. It is also shown here that in patients with abnormal ferritin levels, the frequency of abnormal AR size is 24% higher than in patients whose ferritin levels are within the normal range (73.3 vs. 50). Also, it has been shown that the frequency of abnormal AR size is 12% higher in patients with abnormal Ca levels (84.6 vs. 72.4). In addition, the frequency of abnormal-size AR in patients with abnormal ALP is more than 10% compared to normal ALP levels (83.9 vs. 71.4). Furthermore, patients with higher vitamin D levels have a more normal AR size than patients with vitamin D deficiency; all the above differences were insignificant (all *P* values were ≥ 0.05). Other results are shown in Table 4.

Table 3. The relationship between the levels of ferritin, Ca, ALP, PTH, PLT, and vitamin D with AVA

Variable	AVA		*P* value
	Normal (21 ± 1.8 mm) No. (%)	Abnormal (<19.2, >22.8 mm) No. (%)	
Ferritin			0.06
Normal (24–124 mg/dL)	2 (100)	0	
Abnormal (<24, >124 mg/dL)	62 (27.6)	163 (72.4)	
Ca			0.08
Normal (8.2–10.5 mg/dL)	63 (29.4)	151 (70.6)	
Abnormal (<8.2, >10.5 mg/dL)	1 (7.7)	12 (92.3)	
ALP			0.13
Normal (180–1200 IU/L)	59 (30.1)	137 (69.9)	
Abnormal (<180, >1200 IU/L)	5 (16.1)	26 (83.9)	
PTH			0.57
Normal (8–76 pg/mL)	58 (27.6)	111 (64.7)	
Abnormal (<8, >76 pg/mL)	6 (35.3)	52 (72.4)	
PLT			0.53
Normal (150–450)	39 (26.5)	108 (73.5)	
Abnormal (<150, >450)	25 (31.3)	55 (68.7)	
Vitamin D_3			0.58
<20 ng/mL deficient	21 (25)	63 (75)	
20–30 ng/mL insufficient	20 (32.8)	41 (67.2)	
31–100 ng/mL sufficient	23 (29.5)	55 (70.5)	

Abbreviations: Ca, calcium; ALP, alkaline phosphatase; PTH, parathyroid hormone; PLT, platelet; AVA, aortic valve area.

Table 4. The relationship between the levels of ferritin, Ca, ALP, PTH, PLT, and vitamin D with AR

Variable	AR		*P* value
	Normal (21 ± 1.8 mm) No. (%)	Abnormal (<19.2, >22.8 mm) No. (%)	
Ferritin			0.46
Normal (24–124 mg/dL)	1 (50)		
Abnormal (<24, >124 mg/dL)	60 (26.7)	165 (73.3)	
Ca			0.52
Normal (8.2–10.5 mg/dL)	59 (27.6)	155 (72.4)	
Abnormal (<8.2, >10.5 mg/dL)	2 (15.4)	11 (84.6)	
ALP			0.19
Normal (180–1200 IU/L)	56 (28.6)	140 (71.4)	
Abnormal (<180, >1200 IU/L)	5 (16.1)	26 (83.9)	
PTH			1
Normal (8–76 pg/mL)	57 (27.1)	153 (72.9)	
Abnormal (<8, >76 pg/mL)	4 (23.5)	13 (76.5)	
PLT			0.87
Normal (150–450)	39 (26.5)	108 (73.5)	
Abnormal (<150, >450)	22 (27.5)	58 (72.5)	
Vitamin D_3			0.96
<20 ng/mL deficient	23 (27.4)	61 (76.2)	
20–30 ng/mL insufficient	16 (26.2)	45 (73.8)	
31–100 ng/mL sufficient	22 (28.2)	56 (71.8)	

Abbreviations: Ca, calcium; ALP, alkaline phosphatase; PTH, parathyroid hormone; PLT, platelet; AR, aortic root.

Discussion

According to the results obtained from the present study, the average serum ferritin in the examined patients was higher than normal. However, serum vitamin D was lower than normal, and other hematological indicators were within normal range. Also, in the echocardiographic evaluation, more than half of the patients had heart failure, and more than one-third had aortopathy. In other similar studies, heart complications in thalassemia major patients were reported as among the main complications of these patients. For example, in the study by Oztarhan et al, the ventricular dysfunction index in patients with thalassemia major was reported to be higher than in healthy individuals (17). Also, in an analytical study, the diastolic function of the heart of patients with thalassemia major was compared with a control group, and the results showed that the diastolic function was impaired before the systolic function was impaired (18). In Chahkandi and colleagues' study, left ventricular diastolic dysfunction was the most common finding in echocardiography of patients with thalassemia major (19). Cardiac disorders in thalassemia patients are mainly attributed to iron overload. Previous studies have also shown iron overload in thalassemia patients (20). Based on confirmed hypotheses, iron accumulation in cells causes the initiation of the Fenton and Haber-Weiss reactions and the production of superoxide, hydrogen peroxide (H2O2), and hydroxyl radicals in cells. Hydroxyl radical, a strong oxidizer, can cause cell membrane permeability and lipid peroxidation changes. These changes will also cause the leakage of hydrolytic enzymes, cell damage, and subsequent cardiac myocyte death. In cases with myocardial ischemia, iron overload can accelerate the reperfusion disorder caused by ischemia, and this causes an autocatalytic process and ultimately leads to cardiomyopathy (21,22). In addition, according to studies, iron overload reduces cardiac function; however, many patients are asymptomatic despite the high volume of cardiac iron storage (23). These studies' results are consistent with our study's results, i.e., with an increase in serum ferritin levels in the present study, abnormality occurred in all three criteria for evaluating cardiac function, including EF, AR, and AVA.

Also, Saadatifar et al showed that in thalassemia patients, there is an inverse relationship between the increase in iron levels and vitamin D serum levels, which can cause cardiac dysfunction (24).

In addition, Koca Yozgat et al showed that thalassemia patients have cardiac dysfunction and deficiencies in vitamin D levels (25).

Although the studies show that parathyroid levels and, subsequently, Ca levels are low in patients with beta-thalassemia, some studies have found a significant negative relationship between high ferritin levels and parathyroid function (26). However, some studies have proposed a new hypothesis concerning beta-thalassemia patients. Saki et al and Dejkhamron et al hypothesized that high ferritin levels in thalassemia patients may stimulate PTH secretion in normal parathyroid function. As a result, PTH and serum Ca are normal (27,15). In another study with a larger sample size, a direct relationship between ferritin and PTH levels was observed (12,15). The present study's findings are also in line with this hypothesis, i.e., most of the studied subjects had normal parathyroid function and Ca. However, the vitamin D levels in most of the patients in this study were below the normal range.

Although the lack of vitamin D in these patients can be due to the reduction of outdoor activities, genetic and ethnocultural factors, dark skin, or wearing clothing that reduces sun exposure (15), hepatic dysfunction of vitamin D-25OH hydroxylation and secondary chronic renal disease caused by iron overload have also been mentioned as essential causes of vitamin D conversion disorder in its active form in patients with thalassemia (10,28). In addition, the role of fibroblast growth factor 23 (FGF23) in suppressing the production of this vitamin in the kidney has also been considered (29). Studies have shown that vitamin D directly and indirectly affects the cardiovascular system (30,31). Some past studies have observed a direct relationship between vitamin D deficiency and heart function. In Wood and colleagues' study, a positive direct relationship was observed between LVEF and the amount of 25-hydroxyvitamin D and the D25-OH/D1-25OH ratio (10). Also, in the results of other studies, it has been shown that vitamin D deficiency in thalassemia major patients is related to cardiac cytological disorders and causes increased inflammation and inflammatory cytokines, fibrosis, and oxidative stress, leading to cardiac disorders in this group of patients. (32-34).

Additionally, it has been demonstrated in the findings of other studies that vitamin D deficiency in patients with thalassemia major is associated with cardiac cytological disorders, increases inflammation and inflammatory cytokines, causes fibrosis, and increases oxidative stress, all of which contribute to cardiac disorders in these patients. However, our investigation found no association between vitamin D levels and heart function indicators. Other factors like anemia and high ferritin levels have a more significant effect. Also, there was no association between vitamin D levels and cardiac function in Dejkhamron and colleagues' study (15). However, this discrepancy can be attributed to the small sample size.

According to a review of studies, parathyroid levels and Ca levels are low in patients with beta-thalassemia (36). However, parathormone hormone levels in the current study were within normal range. Thus, the normal Ca level in the patients examined in the current study is acceptable. In addition, due to the importance of Ca homeostasis, its amount is controlled by specific systems to be maintained within the normal range (37). It is recommended to test bone mineral density in the following examinations to assess the body's Ca levels.

In general, the sample size in the current study was low, which is one possible reason for the lack of significant relationships.

Conclusion

The findings of this study demonstrated that a considerable proportion of thalassemia major patients have cardiac failure and aortopathy. Furthermore, the frequency of cardiac complications was lower in patients without vitamin D and Ca deficiency. However, some of these results were insignificant, possibly due to the small sample size and short duration of the current study.

Acknowledgements

We thank Afzalipour Clinical Research Development Unit for their cooperation.

Authors' Contribution

Conceptualization: Maryam Ahmadipour, Elham Maleki.
Data curation: Maryam Ahmadipour, Elham Maleki.
Formal analysis: Ahamd Naghibzadeh-Tahami.
Funding acquisition: Maryam Ahmadipour.
Investigation Maryam Ahmadipour, Koroush Mirzie.
Methodology: Ahamd Naghibzadeh-Tahami.
Project administration: Maryam Ahmadipour.
Resources: Maryam Ahmadipour.
Software: Ahamd Naghibzadeh-Tahami.
Supervision: Maryam Ahmadipour.
Validation: Maryam Ahmadipour, Ahamd Naghibzadeh-Tahami.
Visualization: Ahamd Naghibzadeh-Tahami.
Writing–original draft: Maryam Ahmadipour, Elham Maleki.
Writing–review & editing: Ahamd Naghibzadeh-Tahami, Koroush Mirzaie.

Competing Interests

The authors declare no conflict of interest regarding the study.

Disclaimers

This publication is not affiliated with any specific institution or organization, and the authors are solely responsible for its content.

Ethical Approval

This study was approved by the Ethics Committee of Kerman University of Medical Sciences with the ethical code IR.KMU.AH.REC.1397.169. Furthermore, informed written consent was obtained from all participants. The necessary information about the study process was provided to them, and all questions about the study asked by the participants were answered.

Funding

This research received no specific grant from public, commercial, or not-for-profit funding agencies.

References

1. Rachmilewitz EA, Giardina PJ. How I treat thalassemia. Blood. 2011;118(13):3479-88. doi: 10.1182/blood-2010-08-300335.

2. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis. 2010;5:11. doi: 10.1186/1750-1172-5-11.
3. Shiri R, Mahdieh N. An overview on thalassemia: genetics of beta thalassemia in Iran. Koomesh. 2005;17(1):1-17. [Persian].
4. Khorasani G, Kosaryan M, Vahidshahi K, Shakeri S, Nasehi MM. Results of the national program for prevention of beta-thalassemia major in the Iranian province of Mazandaran. Hemoglobin. 2008;32(3):263-71. doi: 10.1080/03630260802004269.
5. Miri M, Tabrizi Namini M, Hadipour Dehshal M, Sadeghian Varnosfaderani F, Ahmadvand A, Yousefi Darestani S, et al. Thalassemia in Iran in last twenty years: the carrier rates and the births trend. Iran J Blood Cancer. 2013;6(1):11-7. [Persian].
6. Fahim FM, Saad K, Askar EA, Eldin EN, Thabet AF. Growth parameters and vitamin D status in children with thalassemia major in upper Egypt. Int J Hematol Oncol Stem Cell Res. 2013;7(4):10-4.
7. Betts M, Flight PA, Paramore LC, Tian L, Milenković D, Sheth S. Systematic literature review of the burden of disease and treatment for transfusion-dependent β-thalassemia. Clin Ther. 2020;42(2):322-37.e2. doi: 10.1016/j.clinthera.2019.12.003.
8. Jamshidi K, Abdollahzad H, Nachvak M, Rezaei M, Golpayegani MR, Sharifi Zahabi E. Effects of alpha-lipoic acid supplementation on cardiovascular disease risk factors in β-thalassemia major patients: a clinical trial crossover study. J Blood Med. 2020;11:131-9. doi: 10.2147/jbm.s252105.
9. Khamseekaew J, Kumfu S, Chattipakorn SC, Chattipakorn N. Effects of iron overload on cardiac calcium regulation: translational insights into mechanisms and management of a global epidemic. Can J Cardiol. 2016;32(8):1009-16. doi: 10.1016/j.cjca.2015.10.012.
10. Wood JC, Claster S, Carson S, Menteer JD, Hofstra T, Khanna R, et al. Vitamin D deficiency, cardiac iron and cardiac function in thalassaemia major. Br J Haematol. 2008;141(6):891-4. doi: 10.1111/j.1365-2141.2008.07135.x.
11. de Vernejoul MC, Girot R, Gueris J, Cancela L, Bang S, Bielakoff J, et al. Calcium phosphate metabolism and bone disease in patients with homozygous thalassemia. J Clin Endocrinol Metab. 1982;54(2):276-81. doi: 10.1210/jcem-54-2-276.
12. Gözü Pirinççioğlu A, Gökalp D, Söker M. Parathyroid functions in thalassemia major patients. Ann Clin Endocrinol Metab. 2017;1:15-9. doi: 10.29328/journal.acem.1001003 .
13. Pala M, Bhat KG, Manya S, Joseph N, Harish S. Vitamin D levels and left ventricular function in beta-thalassemia major with iron overload. Eur J Pediatr. 2023;182(4):1749-54. doi: 10.1007/s00431-023-04830-7.
14. Pilz S, Kienreich K, Tomaschitz A, Lerchbaum E, Meinitzer A, März W, et al. Vitamin D and cardiovascular disease: update and outlook. Scand J Clin Lab Invest Suppl. 2012;243:83-91. doi: 10.3109/00365513.2012.681972.
15. Dejkhamron P, Wejaphikul K, Mahatumarat T, Silvilairat S, Charoenkwan P, Saekho S, et al. Vitamin D deficiency and its relationship with cardiac iron and function in patients with transfusion-dependent thalassemia at Chiang Mai University Hospital. Pediatr Hematol Oncol. 2018;35(1):52-9. doi: 10.1080/08880018.2018.1424280.
16. Ozdemir O, Olgunturk R, Kula S, Tunaoglu FS. Echocardiographic findings in children with Marfan syndrome. Cardiovasc J Afr. 2011;22(5):245-248. doi:10.5830/CVJA-2010-085.
17. Oztarhan K, Delibas Y, Salcioglu Z, Kaya G, Bakari S, Bornaun H, et al. Assessment of cardiac parameters in evaluation of cardiac functions in patients with thalassemia major. Pediatr Hematol Oncol. 2012;29(3):220-34. doi: 10.3109/08880018.2012.671449.
18. Ghaemian A, Hoseini A, Kosarian M. Left ventricular diastolic abnormalities in thalassemia major with normal systolic function. Med J Islam Repub Iran. 2002;16(1):9-12.
19. Chahkandi T, Kazemi T, Jalili A, Ghaderi F. Evaluation of cardiac function in patients with major beta thalassemia in Birjand. Sci J Iran Blood Transfus Organ. 2013;10(1):86-92. [Persian].
20. Taher AT, Saliba AN. Iron overload in thalassemia: different organs at different rates. Hematology Am Soc Hematol Educ Program. 2017;2017(1):265-71. doi: 10.1182/asheducation-2017.1.265.
21. Jian J, Yang Q, Dai J, Eckard J, Axelrod D, Smith J, et al. Effects of iron deficiency and iron overload on angiogenesis and oxidative stress-a potential dual role for iron in breast cancer. Free Radic Biol Med. 2011;50(7):841-7. doi: 10.1016/j.freeradbiomed.2010.12.028.
22. Kabat GC, Rohan TE. Does excess iron play a role in breast carcinogenesis? An unresolved hypothesis. Cancer Causes Control. 2007;18(10):1047-53. doi: 10.1007/s10552-007-9058-9.
23. Wood JC, Enriquez C, Ghugre N, Otto-Duessel M, Aguilar M, Nelson MD, et al. Physiology and pathophysiology of iron cardiomyopathy in thalassemia. Ann N Y Acad Sci. 2005;1054:386-95. doi: 10.1196/annals.1345.047.
24. Saadatifar H, Mohaghegh H, Ahmadi M, Moshkani farahani M. Relationship between the plasma levels of vitamin D and magnesium and cardiac involvement and iron overload in thalassemia major patients referred to Ganjavian Hospital of Dezful in 2018. Iran Heart J. 2021;22(4):15-24.
25. Koca Yozgat A, Azak E, Kaçar D, Işık M, Arman Bilir Ö, Güzelküçük Z, et al. The effects of vitamin D on myocardial function demonstrated by speckle-tracking echocardiography in children with beta thalassemia. Turk Kardiyol Dern Ars. 2023;51(5):328-32. doi: 10.5543/tkda.2023.85265.
26. Hagag AA, El-Shanshory MR, Abo El-Enein AM. Parathyroid function in children with beta thalassemia and correlation with iron load. Adv Pediatr Res. 2015;2(3):1-6. doi: 10.12715/apr.2015.2.3.
27. Saki F, Salehifar A, Kassaee SR, Ranjbar Omrani G. Association of vitamin D and FGF23 with serum ferritin in hypoparathyroid thalassemia: a case control study. BMC Nephrol. 2020;21(1):482. doi: 10.1186/s12882-020-02101-3.
28. Manolopoulos PP, Lavranos G, Mamais I, Angouridis A, Giannakou K, Johnson EO. Vitamin D and bone health status in beta thalassemia patients-systematic review. Osteoporos Int. 2021;32(6):1031-40. doi: 10.1007/s00198-021-05821-w.
29. Saki F, Ranjbar Omrani G. Evaluation of serum fibroblast growth factor-23 in patients with beta-thalassemia major compared to healthy population. Iran J Pediatr Hematol Oncol. 2022;12(3):182-9. doi: 10.18502/ijpho.v12i3.10061.
30. Nitsa A, Toutouza M, Machairas N, Mariolis A, Philippou A, Koutsilieris M. Vitamin D in cardiovascular disease. In Vivo. 2018;32(5):977-81. doi: 10.21873/invivo.11338.
31. Guessous I, Bochud M, Bonny O, Burnier M. Calcium, vitamin D and cardiovascular disease. Kidney Blood Press Res. 2011;34(6):404-17. doi: 10.1159/000328332.
32. Pishgahi M, Niroomand M, Bozorgmehr R, Ghane-Fard S, Mousavi F, Tabary M, et al. Association between serum vitamin D level and echocardiographic abnormalities in patients with thalassemia major. Cardiovasc Hematol Disord Drug Targets. 2020;20(3):214-20. doi: 10.2174/1871529x20666200701104931.
33. Wood JC. Cardiac complications in thalassemia major. Hemoglobin. 2009;33(Suppl 1):S81-6. doi: 10.3109/03630260903347526.
34. Rai V, Agrawal DK. Role of vitamin D in cardiovascular diseases. Endocrinol Metab Clin North Am. 2017;46(4):1039-59. doi: 10.1016/j.ecl.2017.07.009.
35. Goyal M, Abrol P, Lal H. Parathyroid and calcium status in patients with thalassemia. Indian J Clin Biochem. 2010;25(4):385-7. doi: 10.1007/s12291-010-0071-5.
36. Pu F, Chen N, Xue S. Calcium intake, calcium homeostasis and health. Food Sci Hum Wellness. 2016;5(1):8-16. doi: 10.1016/j.fshw.2016.01.001.