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Vitamin D Status in Children with Thalassemia Major

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ABSTRACT

Objective: To determine the vitamin D status in children with transfusion dependent beta thalassemia major attending outpatient department of Military hospital of Rawalpindi.
Study Design: Cross sectional study.
Place and Duration of Study: Outpatient Department, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Jan to Oct 2020.
Methodology: All transfusion dependent beta-thalassemia major patients irrespective of age and sex were consecutively enrolled. Serum 25-hydroxy vitamin D3 (25(OH)D3) level was measured for the assessment of vitamin D status. Vitamin D sufficiency was defined as serum level of 25-OHD >30 ng/ml, vitamin D insufficiency was defined as serum 25-OHD 30-20 ng/ml, while vitamin D deficiency was defined as serum 25-OHD <20-10 ng/ml.
Results: Of 162 children, 79(48.8%) were males and 83(51.2%) were females. The mean age was 5.8±2.63 years. Vitamin D deficiency was observed in 43(26.5%) patients, vitamin D insufficiency in 85(52.5%), while vitamin D sufficiency in 34(21.0%) patients with (*p*-value <0.352). A statistically significant association of vitamin D status was observed with regular use of vitamin D supplementation (*p*-value <0.001), calcium supplementation (*p*-value <0.001) and bone pains (*p*-value of <0.001). Type of iron chelation and serum ferritin level (*p*-value <0.001) were also found to be statistically significant. Association of vitamin D level with regular blood transfusion and frequency of blood transfusion was not found to be statistically significant (*p*-value<0.231).
Conclusion: Children with beta thalassemia had a significant prevalence of vitamin D insufficiency, which contributes to bone damage.

Keywords: Children, Transfusion Dependent Thalassemia Major, Vitamin D Status.

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INTRODUCTION

Thalassemia a major public health issue is considered the most frequent single-gene disorder all over the world. β-Thalassemia major (β-TM) is seen with a mutation in the gene for β-hemoglobin, and the mutation may be homozygous or compound heterozygous.[1]

Although great progress has been achieved in the affluent nations in terms of thalassemia prevention and management, this is not the case in many of the middle-income and poorer countries.[2] In Southeast Asia, there are 20,420 predicted infants with β-thalassemia per year.[3] In Pakistan, more than 5% people are thalassemia carrier.[4] Moreover, 5000 children every year diagnosed with thalassemia.[4]

A lifelong treatment of beta thalassemia is repeated blood transfusions.[5] The progressive iron overload in beta thalaseemia major patients is the consequences of ineffective erythropoiesis increase git absorption and above all multiple blood transfusion. Excess iron deposits within organs which include liver, lungs heart and endocrine glands. Recently, life quality and expectancies of patients with β-TM have greatly improved due to modified protocols of blood transfusions and chelating therapy.[6,7] However, studies have shown that osteopenia and osteoporosis along with other various complication.[7,8]

Although there is no official national registry available, it is estimated that approximately 5 to 9 thousand Pakistani children with thalassemia major are born annually. There are around 9.8 million carriers with the rate being 5-7% in the entire population.[9] Similarly, recent local data of the vitamin D status in this population is also lacking. It is stated that genetic and ethno-cultural factors, such as dark skin or concealing clothing, increase the risk of

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vitamin D deficiency. Moreover, reduced outdoor activity in thalassemic patients can also impair cutaneous vitamin D synthesis.

With this background in mind, aim of our study is to identify the vitamin D status of patients diagnosed with (β-TM), who are transfusion dependent and calculate the prevalence of vitamin D deficiency and insufficiency in (β-TM) population, in a large cosmopolitan city of Pakistan. This will allow us to reasonably devise policy frameworks to screen and supplement vitamin D to minimize the morbidity associated with vitamin D insufficiency/deficiency.

METHODOLOGY

This cross-sectional study was carried out at Outpatient department of Pak Emirates Military Hospital (PEMH) Rawalpindi from November 2020 to June 2021. Approval from the ethical committee of Pak Emirates Hospital was obtained prior conducting of the study. Moreover, signed informed consent was also obtained from all guardians/parents of all study participants prior enrolment in the study.

Inclsuion Criteria: All transfusion dependent beta-thalassemia major (BTM) patients irrespective of age and sex were enrolled through non-probability consecutive sampling.

Exclsuion Criteria: Patients with beta-thalassemia minor or intermedia were excluded.

Thalassemia major was diagnosed by haemoglobin electrophoresis showing Hbf (fetal hemoglobin) equal or more than 95%. All cases were getting iron chelation.

A sample size of 162 children was calculated using Epi Info sample size calculator considering confidence interval 95%, margin of error 5%, reported prevalence of severe deficiency in beta-thalassemia major patients 12%.[10]

Serum 25-hydroxy vitamin D3 (25(OH)D3) level was measured for the assessment of vitamin D status. The presence of serum level of 25-OHD >30 ng/ml was classified as vitamin D sufficiency, serum 25-OHD 30-20 ng/ml was classified as vitamin D insufficiency, serum 25-OHD <20-10 ng/ml was classified as vitamin D deficiency. All patients receiving iron chelation after 1 year of blood transfusion and maintaining serum ferritin level of <1000ng/dL was labeled as regular iron chelated. Furthermore, serum calcium level, serum phosphorus level, and serum ferritin level were also measured. This information along with demographic characteristics like age, sex, age at the time of 1st transfusion, number of transfusions, and regular use of iron chelation therapy were recorded in a pre-designed proforma. None of the patients enrolled in this study had a history of splenectomy.

Statistical analysis for social sciences (SPSS) version 22 was used for data analysis. All quantitative variables like age, age at the time of 1st blood transfusion, number of transfusions per year, duration of blood transfusion, serum vitamin D level, serum calcium level, phosphorus level, and serum ferritin level were explored using mean. Frequency and percentages were calculated for gender, use of iron chelation therapy, and vitamin D status. Inferential statistics were explored using chi-square test. The *p*-value of ≤0.05 was considered as significant.

RESULTS

Of 162 patients, vitamin D deficiency was observed in 43(26.5%) patients, vitamin D insufficiency in 85(52.5%), while vitamin D sufficiency in 34(21.0%) patients. (Figure-I)

The median age of the patients was 6(3-8) years. Furthermore, the median age at the time of diagnosis, median age at time of first transfusion, frequency of transfusion per day, and total number of transfusions so far were found to be 8(7-9) years, 6(5-7), and 25(20-30), and 74(42-99) respectively.

An insignificant median difference of vitamin D status was observed with age at the time of diagnosis (*p*-value 0.154), age at the time of 1st transfusion (*p*-value 0.069), frequency of transfusion per day (*p*-value 0.484), and total transfusion dose so far (*p*-value 0.203). There were 79(48.8%) males and 83(51.2%) females. A significant association of vitamin D status was observed with regular use of vitamin D supplementation (*p*-value <0.001), regular use of calcium supplementation (*p*-value <0.001), regular use of iron chelation (*p*-value <0.001), and history of bone pain (*p*-value <0.001). (Table)

None of the patients enrolled in this study had a history of splenectomy.

The overall median serum calcium level and serum ferritin level was found to be 2.2(2.1-2.3) mg/dL and 2681(2000-3297) ng/ml respectively. A significant median difference of serum calcium level was found with respect to vitamin D status (*p*-value <0.001) whereas serum ferritin level was found to be insignificant (*p*-value 0.140).

Most of the patients were regularly using iron chelation therapy, i.e., 92(56.8%). A significant median difference of vitamin D level was observed with regularly use of iron chelation therapy (*p*-value <0.001). (Figure-II)

Table: Comparison of Vitamin D status with baseline characteristics of the thalassemia major patients (n=162)

	Overall (n=162)	Deficiency (n=23)	Insufficiency (n=11)	Sufficiency (n=128)	
	median (IQR)	Median (IQR)	median (IQR)	median (IQR)	*p*-value
Age, years	6(3-8)	6(3-8)	7(4-8)	5(3-8)	0.154α
Age at the time of diagnosis, years	8(7-8)	8(6-8)	8(7-9)	8(7-10)	0.069α
Age at the time of 1st transfusion, years	6(5-7)	6(6-7)	6(5-7)	6(5-7)	0.235α
Frequency of transfusion per day	25(20-30)	25(20-30)	25(20-30)	25(20-30)	0.484α
Total transfusion dose so far	74(42-99)	66(45-91)	80(42-110)	59(30-95)	0.203α
	n(%)	n(%)	n(%)	n(%)	*p*-value
Gender					
Male	79	18(22.8)	46(58.2)	15(19.0)	0.352¥
Female	83	25(30.1)	39(47.0)	19(22.9)	
Regular use of vitamin D supplementation					
Yes	107	10(9.3)	64(59.8)	33(30.8)	<0.001¥
No	55	33(60.0)	21(38.2)	1(1.8)	
Regular use of Calcium supplementation					
Yes	138	27(19.6)	78(56.5)	33(23.9)	<0.001¥
No	24	16(66.7)	7(29.2)	1(4.2)	
Regular use of iron chelation therapy					
Yes	92	14(15.2)	57(62.0)	21(22.8)	<0.001¥
No	70	29(41.4)	28(40.0)	13(18.6)	
History of bone pain					
Yes	64	38(59.4)	25(39.1)	1(1.6)	<0.001¥
No	98	5(5.1)	60(61.2)	33(33.7)	

aKruskal-Wallis Test applied, ¥Chi-square test applied, p-value ≤0.05 taken as significant

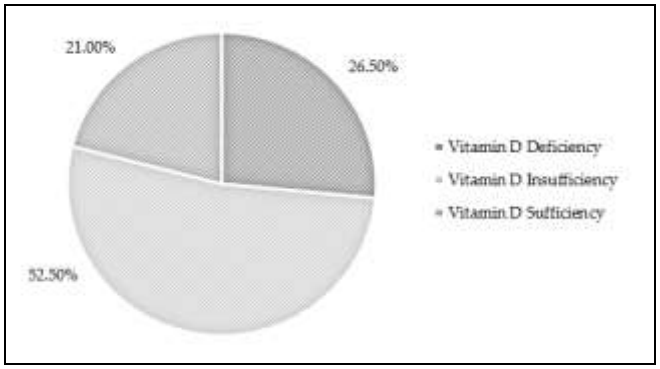

Figure-1: Vitamin D status of the patients with beta thalassemia major (n=162)

DISCUSSION

Within our sample of 162 patients, vitamin D deficiency was observed in 26.5% patients, vitamin D insufficiency in 52.5%, while vitamin D sufficiency in 21.0% patients. The current study had a higher prevalence of Vitamin D deficiency as compared Fatima *et al.*,[11] which also surveyed Pakistani population and found 3.1% of their sample to be deficient. In contrast Ahmed *et al.*,[9] had a higher percentage of deficiency (72.2%) while surveying beta thalassemia major children and adolescents. Similar studies done outside Pakistan also observed that a majority of patients were Vitamin D deficient.[12,13] According to a study conducted by Vogiatzi *et al.*,[14] it was reported that about 12.8% of the patients had deficient and 82% insufficient levels of Vitamin D. The trends of Vitamin D deficiency vary greatly in different parts of the world. Our analysis also gave a significant association of vitamin D status with regular use of iron chelation therapy, regular use of vitamin D therapy, regular use of calcium, and history of bone pain.

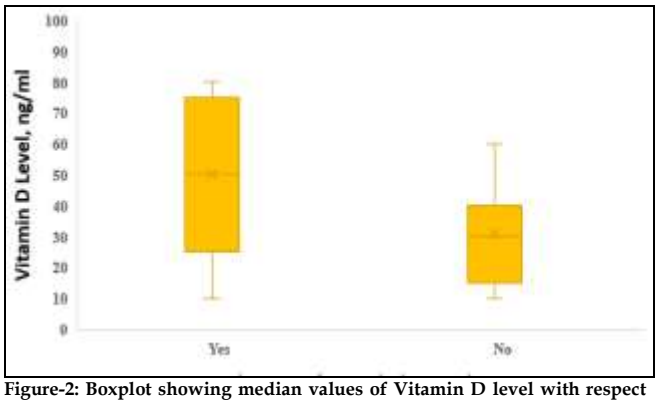

Figure-2: Boxplot showing median values of Vitamin D level with respect to regular use of iron chelation therapy

It is reported in literature that vitamin D is generally involved in calcium metabolism.[13] Serum 25-OHD levels less than 30 ng/dl is associated with a significant decrease in calcium absorption in the intestines15. Only 10-15% of dietary calcium is absorbed when vitamin D is absent.[16] In a study by Humayun *et al.*, a positive correlation between vitamin D and serum calcium was observed in thalassemia patients.[17] Similarly, our study showed a significant correlation between these vitamin D and calcium level.

Variable findings were observed in studies conducted in other parts of the world.[18,19] The use of chelation therapy for iron overload in transfusion dependent thalassemia major patient is strongly recommended.[20] Moreover, phosphorus is a crucial component of cell membranes and plays an important role in energy production, acid-base hemostasis and phosphorylation reactions. Phosphorus levels in the body, just like calcium are regulated by vitamin D and PTH.[21-24]

Furthermore, the demographics characteristics of the current study resembled with the similar studies done before in Pakistan and in other parts of the world.[11,17,25] An insignificant median difference of vitamin D status was observed with age at the time of diagnosis, age at the time of 1st transfusion, frequency of transfusion per day, and total transfusion dose so far. There is scant reference of these parameters in current literature, and we could not find studies to either support or refute these.

LIMITATION OF STUDY

The findings of the study could be highlighted in the light of limitation that certain important clinical and laboratory variables were not reported. Moreover, treatment plan and outcome also not reported in the current study. Additionally, a more detailed look into variables explored in other studies such as parathyroid hormone levels could have shed light onto suspected associations such as hypoparathyroidism secondary to transfusion dependent thalassemia. Further inquiry and detailed prospective studies appear to be necessary for verification and to probe the suspected connection between vitamin D deficiency and the transfusion regimen received by pediatric patients.

In summation, our study appeared to reinforce previous literature that cited vitamin D deficiency as a major demonstration in patients with thalassemia major, and its particularly strong relation of this deficiency with age. However, the significance with age and frequency of transfusions needs further examination. Vitamin D deficiency can further deteriorate the quality of life of patients already suffering from thalassemia and therefore must be monitored regularly.

CONCLUSION

We concluded that children with beta thalassemia had a significant prevalence of vitamin D insufficiency, which contributes to bone damage. Screening 25 OH-D levels in the blood could help to promote bone mineral accretion and prevent bone disease.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SA & TG: Data acquisition, data analysis, critical review, approval of the final version to be published.

SA & AA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

RN & AR: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Bravo-Urquiola M, Arends A, Gomez G, Montilla S, Gerard N, Chacin M, et al. Molecular spectrum of beta-thalassemia mutations in the admixed Venezuelan population, and their linkage to beta-globin gene haplotypes. Hemoglobin 2012; 36(3): 209–218.
2. Weatherall DJ. The Evolving Spectrum of the Epidemiology of Thalassemia. Hematol Oncol Clin North Am 2018; 32(2): 165-175.
3. Kattamis A, Forni GL, Aydinok Y, Viprakasit V. Changing patterns in the epidemiology of β-thalassemia. Eur J Haematol 2020; 105(6): 692-703.
4. Asif N, Hassan K. Management of thalassemia in Pakistan. J Islamabad Med Dental Coll 2016; 5(4): 152-153.
5. Li XY, Sun X, Chen J, Qin MQ, Luan Z, Zhu YP, et al. Hematopoietic stem cell transplantation for children with β-thalassemia major: multicenter experience in China. World J. Clin. Pediatr 2018; 14(1): 92-99.
6. Chuansumrit A, Pengpis P, Mahachoklertwattana P, Sirachainan N, Poomthavorn P, Sungkarat W, et al. Effect of Iron chelation therapy on glucose metabolism in non-transfusion-dependent Thalassaemia. Acta Haematol 2017; 137(1): 20–26.
7. Baldini M, Marcon A, Ulivieri FM, Seghezzi S, Cassin R, Messina C, et al. Bone quality in beta-thalassemia intermedia: relationships with bone quantity and endocrine and hematologic variables. Ann Hematol 2017; 96(6): 995–1003.
8. Allegra S, Cusato J, De Francia S, Longo F, Pirro E, Massano D, et al. The effect of vitamin D pathway genes and deferasirox pharmacogenetics on liver iron in thalassaemia major patients. Pharmacogenomics J 2019; 19(5): 417-427.
9. Ahmed S, Saleem M, Modell B, Petrou M. Screening extended families for genetic hemoglobin disorders in Pakistan. N Engl J Med. 2010; 347(15): 1162–1168.
10. PK M, Bhagwan B. Biochemical indices and radiological examination to evaluate bone health in children with β-thalassemia major. Int J Contemp Pediatr. 2019; 6(2): 549.
11. Fatima I, Yaqub N, Anwar T, Nisar YB, Khalid S, Gilani S. Prevalence of Endocrine Complications in Transfusion-Dependent Beta Thalassemic Pakistani Patients. Int J Pathol 2014; 12(2): 77-82.
12. Sultan S, Irfan SM, Ahmed SI. Biochemical Markers of Bone Turnover in Patients with β-Thalassemia Major: A Single Center Study from Southern Pakistan. Adv Hematol 2016; 5437609.
13. Ali GS, Najeeb MK, Jubrail AM, Selamoğlu Z. A Study of Vitamin D and Calcium Level in Beta Thalassemia Major in Duhok Province. Turkish J Agriculture-Food Sci Tech 2019; 7(11): 1924-1927.
14. Vogiatzi MG, Macklin EA, Trachtenberg FL, Fung EB, Cheung AM, Vichinsky E, et al. Differences in the prevalence of growth, endocrine and vitamin D abnormalities among the various thalassaemia syndromes in North America. Br J Haematol 2009; 146(5): 546-556.
15. Soliman A, De Sanctis V, Yassin M. Vitamin d status in thalassemia major: an update. Mediterr J Hematol Infect Dis. 2013; 5(1): e2013057.
16. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006; 81(3): 353-373.
17. Hamayun T. Assessment of vitamin D and calcium levels in multi transfused β-thalassemia syndrome patients of district Peshawar. Adv Basic Med Sci 2017; 1(2): 41-47.
18. Izzah AZ, Rofinda ZD, Arbi F. Vitamin D and Parathyroid Hormone Levels and Their Relation to Serum Ferritin Levels in

Children with Thalassemia Major: One-Center Study in Western Indonesia. J Adv Med Pharmaceutical Sci 2017; 15(1): 1-5.
19. 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): 10-14.
20. Saki F, Salehifar A, Kassaee SR, Omrani GR. Association of vitamin D and FGF23 with serum ferritin in hypoparathyroid thalassemia: a case control study. BMC Nephrol 2020; 21(1): 1-8.
21. Ansari SH, Lassi ZS, Khowaja SM, Adil SO, Shamsi TS. Hydroxyurea (hydroxycarbamide) for transfusion-dependent β-thalassaemia. Cochrane Database Syst Rev 2019; 3(3): CD012064.
22. Hall JE. Guyton and Hall: textbook of medical physiology. ed. 13th, Jordan: Elsevier; 2017.
23. Ozturk Z, Genc GE, Gumuslu S. Minerals in thalassaemia major patients: An overview. J Trace Elements Med Biol 2017; 41(1): 1-9.
24. El-Nashar M, Mortagy AK, El-Beblawy NM, El-Gohary E, Kamel IM, Rashad M, et al. Parathyroid hormone in pediatric patients with β-thalassemia major and its relation to bone mineral density; a case control study. Egyptian J Med Human Genetics 2017; 18(1): 75-78.
25. Aslam M, Khan F, Haq S, Metabolic Abnormalities in Patients with Beta Thalessemia Major. J Sharif Med Dental Coll 2018; 4(01): 3-7.

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