Research Article

A comparative study of 25 hydroxy vitamin D levels in patients of thalassemia and healthy children

Agrawal A[1], Garg M[2], Singh J[3], Mathur P[4], Khan K[5]

[1]Dr. Anika Agrawal, Resident, [2]Dr Manisha Garg, Senior Resident, [3]Dr. Jagdish Singh, Ex. Head of Department, [4]Dr Priyanshu Mathur, Assistant professor, [5]Dr. Khurshida Khan, Senior Resident, all authors affiliated with Department of Paediatrics, SMS Medical College, Jaipur, Rajasthan, India.

Address for Correspondence: Dr. Manisha Garg. E-Mail: drgargmanisha@gmail.com

Abstract

Introduction: Vitamin D deficiency is emerging threat to patients with thalassemia. Adequate circulating levels of vitamin D are essential for optimal skeletal health and reducing fracture risk. The aim of this study was to evaluate the 25-OH- vitamin D levels in patients of thalassemia and compare its prevalence to healthy children. **Methodology:** In a case control study, 50 patients with beta thalassemia major (aged from 3 to 18 years) were compared with 50 sex and age matched children serves as a control group. Anthropometric measurement, Serum level of calcium, phosphorus, alkaline phosphatase, parathyroid hormone and 25-OH-vitamin D (25 hydroxycholecalciferol) were estimated for all patients & controls. **Results:** 25-OH-vitamin D deficiency was observed in 98% cases and 68% in control group. Difference in mean vitamin D levels between cases and controls was statistically significant ($p<0.05$). Weight and body mass index were significantly ($p<0.05$) lower in cases. Patient with beta thalassemia major compare to control had significantly ($p<0.05$) higher level of alkaline phosphatase and parathyroid hormone level. **Conclusion:** Thalassemia is associated with increased prevalence of 25-OH-vitamin D deficiency resulting in poor growth and quality of life in these children. This signifies the importance of therapeutic intervention.

Keywords: Thalassemia major, Calcium, Vitamin D

Introduction

Thalassemia is an inherited autosomal recessive blood disorder of hemoglobin synthesis due to mutations of the globin gene, leading to various degrees of quantitative defect in globin production and reduced synthesis or complete absence of one or more of globin chains, resulting in ineffective erythropoiesis and anemia [1,2].

Their clinical severity widely varies, ranging from asymptomatic forms to severe or even fatal entities. The mainstay of treatment is based on adequate safe blood transfusions and prevention of iron overload. The most accepted blood transfusion protocol aims to increase the concentration of hemoglobin to 13-14 g/dl after transfusion, and maintain it at 9-10 g/dl at all times [1,3]. On the other hand, frequent blood transfusion may cause iron overload which may result in hemosiderosis, the later may be a cause of hypogonadism, diabetes mellitus, hypoparathyroidism and other endocrine abnormalities [4]. The survival of patients with thalassemia major has progressively improved with advances in therapy; however, osteoporosis and cardiac dysfunction remain frequent complications. Adequate circulating levels of vitamin D are essential for optimal skeletal health and reducing fracture risk. Vitamin D is critical for calcium homeostasis and for mineralization of the skeleton, especially during periods of rapid growth, namely infantile and pubertal growth periods.

Vitamin D is transported to the liver and hydroxylated to 25-OH-vitamin D, additional hydroxylation to 1-25-dihydroxy vitamin D3 takes place in the kidney. The major circulating metabolite of vitamin D is serum 25-OH- vitamin D3 [5]. It is the best indicator of vitamin D status and reflects levels from dietary intake and synthesis in the skin [6]. Levels <50 nmol/L (20 ng/ml) are generally considered deficient; levels 52.5-72.5 nmol/L (21-29) ng/ml) are considered insufficient [7].

Manuscript received: 20th July 2016
Reviewed: 7th August 2016
Author Corrected; 20th August 2016
Accepted for Publication: 4th September 2016

Both defective synthesis of 25-OH-vitamin D and/or hypoparathyroidism have been described in thalassemic patients and negatively affect their bone metabolism [8,9].

A report from North India showed prevalence of vitamin D deficiency in around 80% of thalassemic patients [10] and another study from Thailand showed in 90% of thalassemic patients [11]. The aim of this study was to evaluate the 25-OH- Vitamin D levels in patients of thalassemia and compare its prevalence to healthy children.

Material and Methods

Study type, institutional ethical committee permission and patient consent**:**

This case control study was carried out after obtaining ethical committee clearance from the institute. A written consent from all the study patients was taken prior to the study and the patients were briefed about the study in the language they understood.

A total of 50 patients with beta thalassemia major (aged from 3 to 18 years) attending thalassemia center, SPMCHI, SMS Medical College, Jaipur, randomly selected to participate in this case control study during the period from June 2014 to April 2015. The diagnosis of beta thalassemia major was based on standard criteria [12]. All patients included in the study were stable with regular blood transfusions every 1-2 months. Cases with other concomitant disease affecting vitamin D levels and calcium metabolism e.g. chronic kidney disease, celiac or protein energy malnutrition grade 3 and 4 were excluded from the study. Fifty healthy children with comparable age and sex were included as a control group. All cases and controls were not receiving calcium and vitamin D containing preparations.

Full history taking and thorough clinical examination were done for all cases and controls. Anthropometric measurements of patients and controls including weight, height and Z-score were recorded. Body mass index (BMI) was calculated as kg/m2 (Normal BMI = 18.5–24.9, underweight = BMI <18.5 and Overweight BMI = 25–29). Weight was measured in kg (to the nearest 100 grams) using an electronic digital scale.

Height was measured in cm (measured to the nearest mm); children were measured on scales with height gauges, the subject standing with back against the gauge and feet on the weighing platform. All measurements were taken by the same person.

Serum calcium, phosphorus, alkaline phosphatase and parathyroid hormone were estimated. Estimation 25-OH- vitamin D level was done by chemiluminescenceassay using ADIVA CENTOR XP machine.

Statistical analysis: Statistical Package for Social Sciences (SPSS) program version 20 was used for data analysis. The qualitative data were expressed in proportion and percentages and the quantitative data expressed as mean and standard deviations. The difference in proportion was analyzed by using chi square test and the difference in means was analyzed by using student T Test. Correlation analyses were performed using Pearson correlation coefficient. P-value of 0.05 or less was considered significant.

Results

Demographic and clinical data: The mean age of the studied thalassemic patients (16 female and 34 male) and controls (12 female and 38 male) was 9.62 ± 3.51 and 9.83 ± 3.83 years, respectively.

The mean height of cases and controls was 127.36 ± 21.048 cm and 133.44 ± 21.663 cm. Difference was statistically not significant ($p>0.05$). The mean body weight of patients (27.43 ± 17 kg) was significantly ($p<0.05$) lower than that of controls (32.84 ± 12.52 kg). The mean body mass index of cases and controls was 16.27 + 1.86 kg/m^2 and 17.19 ± 1.88 kg/m^2. The difference was statistically significant ($p<0.05$) lower in patients.

Table No. 1: Demographic Parameters in the Thalassemic Patients and Controls.

Variable	Case	Control	Significance
Age (years)	9.62 ± 3.51	9.83 ± 3.83	p>0.05
Height (cm)	9.83 ± 3.83	133.44 ± 21.663	p>0.05
Weight (kg)	27.43 ± 17	32.84 ± 12.52	P<0.05
BMI (kg/m^2)	16.27 ± 1.86	17.1± 91.88	P<0.05

Biochemical studies: Regarding calcium between patients (8.66 ± 0.82 mg/dl) and control (8.60 ±0.91 mg/dl) there was no significant (p>0.05) difference. Mean serum phosphorus level for case and control was 5.20 ±0.61 mg/dl and 5.61±0.59 mg/dl. There was no significant difference (p>0.05). Mean serum alkaline phosphatase value in case and control was 151.32 ± 77.42 IU/L and 102.61±74.34 IU/L respectively. The difference in cases and control was significant (p<0.05) with considerably higher levels in cases. The mean serum parathyroid hormone level of patients and controls was 64.35±16.01 pg/ml and 42.61±13.75 pg/ml respectively. Significantly higher mean was observed among the cases as compared to controls (p <0.05). The mean 25-OH-vitamin D of the studied thalassemic patients and controls was 8.85± 6.687 ng/ml (Range 4 to 45 ng/ml) and 16.86±6.352 ng/ml (Range 4 to 28 ng/ml), respectively. Significantly lower mean was observed among the cases as proportion compared to controls (p <0.05). Proportion of the <20 ng/mL (defeciency of 25-OH- vitamin D) was observed significantly more in cases as compared to controls, (98% vs 68%). No significant correlation was found between 25-OH- vitamin D level and sex.

Table No.-2: Biochemical parameters

VARIABLES	CASE	CONTROL	SIGNIFICANCE
CALCIUM (MG/DL)	8.66 ± 0.82	8.60 ±0.91	P>0.05
PHOSPHORUS (MG/DL)	5.20 ±0.61	5.61±0.59	P>0.05
ALKALINE PHOSPHATASE(IU/L)	151.32 ± 77.42	102.61±74.34	P<0.05
PARATHYROID HORMONE (PG/ML)	64.35± 16.01	42.61± 13.75	P<0.05
VITAMIN D LEVEL (NG/ML)	8.85± 6.687	16	P<0.05

Discussion

Thalassemia patients are subjected to a variety of complications such as growth impairment, endocrinopathy and metabolic abnormalities [4,13,14]. Adequate circulating levels of vitamin D are essential for optimal skeletal health and reducing fracture risk.

Regarding body weight and Body mass index, the mean body weight and Body mass index of our patients was significantly lower than that of controls (Table-1).

Our findings were in agreement with previous studies; Hashemi et al., reported underweight in 45.71% and low body mass index in 18.6% of their patients with B thalassemia major [15] . Jain et al., found 20% were underweight [16]. Shamshirsaz et al., reported a low body weight compared to controls [17] and Chekir et al., reported weight lateness in their patients by 14.28% [18]. However few reports claimed that the mean body weight and Body mass index of thalassemic patients were in normal range [19].

Regarding serum calcium there was no significant (p>0.05) difference between cases and controls (Table-2). Our results was in against with Shamshirsaz et al.,[17] Zamboni et al.,[20] Aleem et al.,[21] and Autio et al.,[22] who found hypocalcemia in their thalassemic patients. They explained their results by the presence of iron overload and hemosiderosis resulting in endocrinopathies. Regarding phosphorous level; we found that there was no significant difference between patients and controls (Table 2). These results were in agreement with studies reported that phosphorous levels were within the normal range in patients compared to controls [23,24].

The mean serum level of 25-OH-vitamin D was significantly lower in our thalassemic patients than in controls (Table 2), 98% of thalassemic patients had vitamin D deficiency. Rashid merchant et al., found vitamin D deficiency in 62% Indian thalassemia major children and suggested that vitamin D deficiency was nutritional deficiency and defective hydroxylation of vitamin D in liver due to hemochromatosis as all children had high serum ferritin levels [25]. Vogiatzi et al., reported that 12% of thalassemic patients were vitamin D deficient and 69.8% had insufficient levels [26]. In our study prevalence of vitamin D deficiency among healthy controls was also high.

A previous study stated that vitamin D (25-OH Vitamin D) is deficient in thalassemic patients especially in winter than in summer due to geographical attitude, air quality, cloud cover, clothing, time of the day, sun screen use [28].

Others reported that the cause of 25 OH-D deficiency may be due to the iron-overload in the liver rather than the dysfunctions of endocrine tissues [29].

Conclusion

Children with B thalassemia major have delayed growth and metabolic abnormality that signifies the importance of therapeutic interventions. The presence of these abnormalities may be due to iron overload and poor nutritional support.

Monitoring of serum level of 25-OH-vitamin D and early correction of vitamin D deficiency by oral or parental use of vitamin D may significantly improve their bone mineral accretion and prevent bone disease.

Funding: Nil, **Conflict of interes**t: Nil
Permission from IRB: Yes

References

1. Kesse-Adu R, Howard J. Inherited anaemias: sickle cell and thalassaemia. *Medicine*. 2013;41(4): 219–24.

2. Higgs DR, Engel JD, Stamatoyannopoulos G. Thalassaemia. Lancet. 2012 Jan 28;379(9813):373-83. doi: 10.1016/ S0140-6736 (11) 60283-3. Epub 2011 Sep 9.

3. Perrotta S, Gallagher PG, Mohandas N. Hereditary spherocytosis. Lancet. 2008 Oct 18;372(9647):1411-26. doi: 10.1016/S0140-6736(08)61588-3.

4. Satwani H, Raza J, Alam M, et al. Endocrine Complications in Thalassemias: Frequency and Association with Serum Ferritin Levels. *Pak Paediat Assoc* J. 2005;29:113–9.

5. Condamine L, Vztovsnik F, Friedlander G, Menaa C, Garabedian M. Local action of phosphate depletion and insulin-like growth factor–I on in vitro production of 1,25-dihydroxyvitamin D3 by cultured mammalian kidney cells. *J Clin Invest*. 1994;94:1673–1679.

6. Wright NM, Papadea N, Wentz B, Hollis B, Willi S, Bell NH. Increased serum 1,25-dihydroxyvitamin D after growth hormone administration is not parathyroid hormone-mediated. Calcif Tissue Int. 1997 Aug; 61(2):101-37. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society.

7. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jul;96(7):1911-30. doi: 10.1210/jc.2011-0385. Epub 2011 Jun 6.

8. Mahachoklertwattana P, Sirikulchayanonta V, Chuansumrit A, Karnsombat P, Choubtum L, Sriphrapradang A, Domrongkitchaiporn S, Sirisriro R, Rajatanavin R. Bone histomorphometry in children and adolescents with beta-thalassemia disease: iron-associated focal osteomalacia. J Clin Endocrinol Metab. 2003 Aug; 88(8):3966-72.

9. De Sanctis V, Vullo C, Bagni B, Chiccoli L. Hypoparathyroidism in beta-thalassemia major. Clinical and laboratory observations in 24 patients. Acta Haematol. 1992;88(2-3):105-8.

10. Singh K, Kumar R, Shukla A, Phadke SR, Agarwal S. Status of 25-hydroxyvitamin D deficiency and effect of vitamin D receptor gene polymorphisms on bone mineral density in thalassemia patients of North India. Hematology. 2012 Sep;17(5):291-6. doi: 10.1179/ 1607845412Y.0000000017.

11. Nakavachara P, Viprakasit V. Children with hemoglobin E/β-thalassemia have a high risk of being vitamin D deficient even if they get abundant sun exposure: a study from Thailand. Pediatr Blood Cancer. 2013 Oct;60(10):1683-8. doi: 10.1002/pbc.24614. Epub 2013 Jun 3.

12. Giardina PJ, Forget BG. Thalassemia syndromes. In: Hoffman R, Benz EJ, Shattil SS, et al., editors. Hematology: Basic Principles and Practice. 5th ed. Philadelphia, Pa: *Elsevier Churchill Livingstone*; 2008. chap 41.

13. Raiola G, Galati MC, De Sanctis V, Caruso Nicoletti M, Pintor C, De Simone M, Arcuri VM, Anastasi S. Growth and puberty in thalassemia major. J Pediatr Endocrinol Metab. 2003 Mar; 16 Suppl 2: 259-66

14. Bielinski BK, Darbyshire PJ, Mathers L, Crabtree NJ, Kirk JM, Stirling HF, Shaw NJ. Impact of disordered puberty on bone density in beta-thalassaemia major.Br J Haematol. 2003 Jan;120(2):353-8.

15. Hashemi A, Ghilian R, Golestan M, et al. The study of growth in thalassemic patients and its correlation with serum ferritin level. *IJPHO*. 2011;1(4):147–51.

16. Jain M, Sinha RS, Chellani H, Anand NK. Assessment of thyroid functions and its role in body growth in thalassemia major. Indian Pediatr. 1995 Feb; 32(2):213-9.

17. Shamshirsaz AA, Bekheirnia MR, Kamgar M, Pourzahedgilani N, Bouzari N, Habibzadeh M, Hashemi R, Shamshirsaz AA, Aghakhani S, Homayoun H, Larijani B. Metabolic and endocrinologic complications in beta-thalassemia major: a multicenter study in Tehran. BMC Endocr Disord. 2003 Aug 12; 3(1):4.

18. Kassab-Chekir A, Laradi S, Ferchichi S, Haj Khelil A, Feki M, Amri F, Selmi H, Bejaoui M, Miled A. Oxidant, antioxidant status and metabolic data in patients with beta-thalassemia. Clin Chim Acta. 2003 Dec;338(1-2):79-86.

19. Hamed EA, El-Melegy NT. Renal functions in pediatric patients with beta-thalassemia major: relation to chelation therapy: original prospective study. *Ital J Pediatr.* 2010;36:39.

20. Zamboni G, Marradi P, Tagliaro F, Dorizzi R, Tatò L. Parathyroid hormone, calcitonin and vitamin D metabolites in beta-thalassaemia major. Eur J Pediatr. 1986 Apr;145(1-2):133-6.

21. Aleem A, Al-Momen AK, Al-Harakati MS, Hassan A, Al-Fawaz I. Hypocalcemia due to hypo-parathyroidism in beta-thalassemia major patients. Ann Saudi Med. 2000 Sep-Nov;20(5-6):364-6.

22. Vogiatzi MG, Autio KA, Mait JE, Schneider R, Lesser M, Giardina PJ. Low bone mineral density in adolescents with beta-thalassemia. Ann N Y Acad Sci. 2005;1054:462-6.

23. Mahachoklertwattana P, Chuansumrit A, Choubtum L, Sriphrapradang A, Sirisriro R, Rajatanavin R. Bone mineral density in children and young adults with beta-thalassemia trait. J Pediatr Endocrinol Metab. 2002 Nov-Dec;15(9):1531-5.

24. Di Stefano M, Chiabotto P, Roggia C, Garofalo F, Lala R, Piga A, Isaia GC. Bone mass and metabolism in thalassemic children and adolescents treated with different iron-chelating drugs. J Bone Miner Metab. 2004; 22(1):53-7.

25. Merchant R, Udani A, Puri V, D'cruz V, Patkar D, Karkera A. Evaluation of osteopathy in thalassemia by bone mineral densitometry and biochemical indices. Indian J Pediatr. 2010 Sep;77(9):987-91. doi: 10.1007/s 12098-010-0158-2. Epub 2010 Aug 25.

26. Vogiatzi MG Macklin EA, Trachtenberg FL, Fung EB, Cheung AM, Vichinsky E, Olivieri N, Kirby M, Kwiatkowski JL, Cunningham M, Holm IA, Fleisher M, Grady RW, Peterson CM, Giardina PJ; Thalassemia Clinical Research Network. Differences in the prevalence of growth, endocrine and vitamin D abnormalities among the various thalassaemia syndromes in North America. Br J Haematol. 2009 Sep;146(5):546-56. doi: 10.1111/j.1365-2141.2009. 07793.x. Epub 2009 Jul 13.

27. Tsitoura S, Amarilio N, Lapatsanis P, Pantelakis S, Doxiadis S. Serum 25-hydroxyvitamin D levels in thalassaemia. Arch Dis Child. 1978 Apr;53(4):347-8.

28. Pirinççioğlu AG, Akpolat V, Köksal O, Haspolat K, Söker M. Bone mineral density in children with beta-thalassemia major in Diyarbakir. Bone. 2011 Oct; 49(4):819-23. doi: 10.1016/j.bone.2011.07.014. Epub 2011 Jul 23.

…….

How to cite this article?

Agrawal A, Garg M, Singh J, Mathur P, Khan K. A comparative study of 25 hydroxy vitamin D levels in patients of thalassemia and healthy children. Int J Pediatr Res.2016;3(9):652-656.doi:10.17511/ijpr.2016.i09.04.

……..