Journal of Global Scientific Research 8 (10) 2023/ 3298-3306

Contents lists available at www.gsjpublications.com

Journal of Global Scientific Research in Medical and Dental Sciences

journal homepage: www.gsjpublications.com/jourgsr

Assessment of Serum Ferritin, Serum Calcium, and Vitamin D Status in β-thalassemia Major Children and Adolescents in Al Rusafa Side in Baghdad

Noor Basim Jabbar[1], Besma Mohammed Ali[2], Bassam Francis Matti[3]

[1]Public Health Department, Ministry of Health, Baghdad, Iraq.
[2]Community Medicine Consultant, Ghazy Al-Hariri Hospital for Surgical Specialties, Ministry of Health, Baghdad, Iraq.
[3]Consultant Adult Haematologist, Haematology and Bone Marrow Transplantation Centre, Medical City, Baghdad, Iraq.

ARTICLE INFO

Received: 26 Sep 2023,
Revised: 27 Sep 2023,
Accepted: 3 Oct 2023,
Online: 25 Oct 2023

Keywords:
Serum Ferritin, Serum Calcium, Vitamin D, β-thalassemia

ABSTRACT

Background: Beta Thalassemia is a genetic disorder inherited by autosomal recessive and occurs throughout the world, including Iraq. Patients with beta-thalassemia require blood transfusions for life, and this can lead to the accumulation of iron in the skin, kidneys, and liver, resulting in a decrease in vitamin D synthesis. **Methodology:** This cross-sectional study was conducted at the Hereditary Blood Disorder Center in Ibn Al balady Hospital in Al Rusafa side in Baghdad from May to August 2023. The population of this study was children and adolescents diagnosed with beta-thalassemia major and on regular blood transfusions. Serum 25-OH-vitamin D, Serum calcium, and Serum ferritin were assessed in those patients. **Result:** Out of 100 patients involved in this study, (38%) were children and (62%) were adolescents, the male-to-female ratio was 0.52. The mean age of the studied sample was 11.52±4.094 years. The mean 25-OH Vit D level was 24.94±14.66 ng/ml, only 23% of the patients had normal levels of serum vitamin D concentration, 56% had deficient levels and 21% had insufficient levels. The mean serum Ca level was 2.28±0.18 mmol/l, only 19% had low total serum calcium levels, 2% had high levels, and 79% had normal serum calcium levels. The mean serum ferritin level was 3940.48 ± 2287.76 ng/ml, no one had a normal serum ferritin level. **Conclusion:** A high prevalence of 25 hydroxy vitamin D deficiency and insufficiency levels among thalassemia patients is found, so frequent monitoring and appropriate therapeutic interventions to maintain normal levels of serum vitamin D are indicated to improve bone health and quality of life of those patients. Also, high levels of serum ferritin were noted among those patients who need frequent follow-up and proper chelation therapy.

1. Introduction

Thalassemia is a heterogeneous inherited disorder of hemoglobin synthesis due to mutations of the globin gene, leading to ineffective erythropoiesis and anemia (1). Based on the reduced globin chain production thalassemia is classified genetically as -α, -β, -β/HbE or –δβ thalassemia (2). The clinical severity varies widely, ranging from asymptomatic to severe or even fatal forms (3).

Corresponding author:
E-mail addresses: dr.noorbasim2013@gmail.com
doi: 10.5281/jgsr.2023.10039635

Beta thalassemia major (BTM) results from the inheritance of two beta-thalassemia alleles, and it is a severe form (4). Patients having BTM will be dependent on blood transfusion for life. Due to multiple transfusions, the excess iron level in their bodies puts them at risk for iron overload which starts to store in the body in the form of ferritin and this can cause dysfunction of some organs, like; the heart, liver, and many glands like thyroid and parathyroid gland (5), if this iron deposition occurs in the parathyroid gland it may lead to hypoparathyroidism and as a consequence, low serum calcium levels have been seen in such patients and symptoms of hypocalcemia occur; and hence Calcium is an essential mineral for bones and teeth building and maintaining so rickets, osteopenia, and osteoporosis may occur (6). In addition, the evidence shows a significant association between growth failure and high serum ferritin levels in BTM patients (7).

Thalassemia is a global health problem with high prevalence and mortality. Thalassemia affects men and women equally and often occurs in persons from South Europe, the Mediterranean region, the Middle East, Africa, and South and East Asia (8). Previous studies have shown that, worldwide, over 25,500 infants born annually have β-thalassemia that will become transfusion-dependent (9).

In Iraq, the prevalence of beta-thalassemia was 36/100,000 In a single population-based analysis (10)

Vitamin D is a fat-soluble vitamin derived from cholesterol and stored in body fat (11). Vitamin D is critical for calcium homeostasis and mineralization of the skeleton especially during infantile and pubertal growth periods which are periods of rapid growth (12). Vitamin D is carried 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 D and this is the best indicator of vitamin D status (13). Vitamin D deficiency leads to reduced bone mineralization and loss of cortical bone, resulting in osteopenia osteoporosis syndrome (OOS) (14).

This deficiency may occur in thalassemic patients due to iron overload, inadequate nutritional intake, and vitamin D hydroxylation disorders in the liver due to hemochromatosis that causes high serum ferritin levels. A recent review article reveals the prevalence of vitamin D deficiency varies from 24.8 to 80.6% and a lot of countries reported cases of vitamin D deficiency (VDD) in thalassemia children. (15,16,17).

The present study was an attempt to determine the levels of ferritin, calcium, and vitamin D among Beta-thalassemia major patients undergoing repeated multiple blood transfusions and to assess the impact of clinical features of the disease on them.

2. Materials and Methods

A convenient sample of 100 children and adolescents who were diagnosed with β thalassemia major and on regular blood transfusions for the period from May until August 2023 attended The Hereditary Blood Disorder Center in Ibn Al-balady Hospital which is the only thalassemia center in Al Rusafa side of Baghdad aged less than 18 years and who were not complaining from other diseases and were not taking supplementation of calcium and vitamin D were enrolled in the study. All the necessary information regarding the study was explained to the parents and informed consent was taken from the institute and from each patient or parents who were willing to participate in the study

Detailed history and thorough clinical examination were done for each patient included in the study. Demographic and clinical data were obtained. Laboratory tests including Serum calcium, Serum ferritin, and Serum vitamin D level estimation were done.

Serum vitamin D levels greater than 30 ng/ml are considered vitamin D sufficiency, less than 20 ng/ml are defined as vitamin D deficiency, and 20 to 29.9 ng/ml are defined as vitamin D insufficiency (18). Normal total serum calcium concentration is considered 8.8-10.4 mg/dl, and this is equivalent to 4.4-5.2 mEq/l or 2.2-2.6 mmol/l (19). Serum ferritin levels <1000 ng/mL are associated with lower morbidity and mortality in thalassemia-dependent transfusion (TDT) (20).

Data Analysis Statistical Package for Social Sciences (SPSS) program (version 23) was used to

statistically evaluate the study findings. Descriptive statistics was used in the form of frequencies and percentages for categorical data, represented by figures and tables. For qualitative variables, the chi-square test was used. The significance level was set at a p-value of 0.05.

3. Results

A total of 100 patients were included in the study. Their mean age was 11.52±4.094 years, 38% of them were children, and 62% were adolescents. Out of a total 34% of them were males and 66% were female, 92% were suffering from the disease for more than 5 years and 81% regularly were receiving blood every 2 weeks. 82% of patients had their first transfusion before their first year of life, (Table 1).

Table 1: Demographic and clinical features of the studied sample

Variable		NO	%
Age	Children ≤ 10 years	38	38.0
	Adolescents >10 years	62	62.0
Gender	Male	34	34.0
	Female	66	66.0
Duration of disease	≤ 5 years	8	8.0
	>5 years	92	92.0
Frequency of blood transfusion	Each 2 weeks	81	81.0
	Each 3 weeks	12	12.0
	Each 4 weeks	7	7.0
Age of onset of transfusion	< 1 year	82	82
	≥ 1 year	18	18
Total		100	100

Figures 1, 2, and 3 show vitamin D, serum calcium, and serum ferritin levels in thalassemic patients, with 56% complaining of vitamin D deficiency, 21% of insufficiency, and only 23% normal, (Figure 1). While 79% with normal serum calcium levels, 19% with low, and only 2% had high calcium levels, (Figure 2). And more than half of the patients (57%) had serum ferritin levels ranging between 1000-4000 ng/ml, (Figure 3).

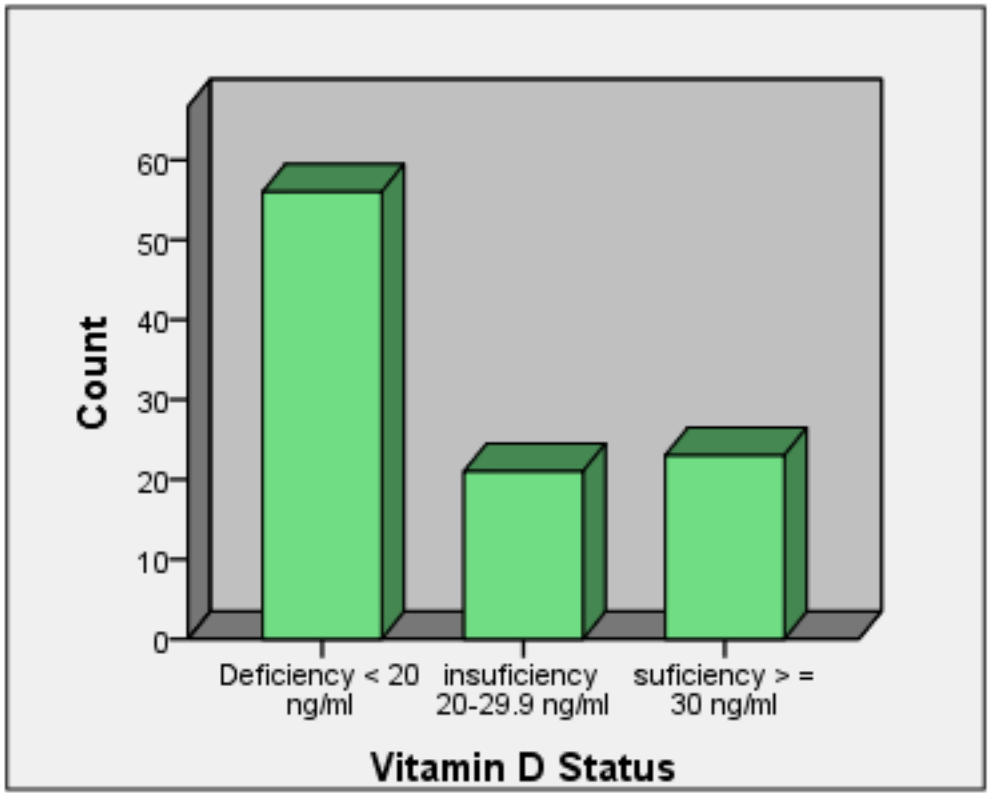

Figure 1: Vitamin D Status in thalassemic patients

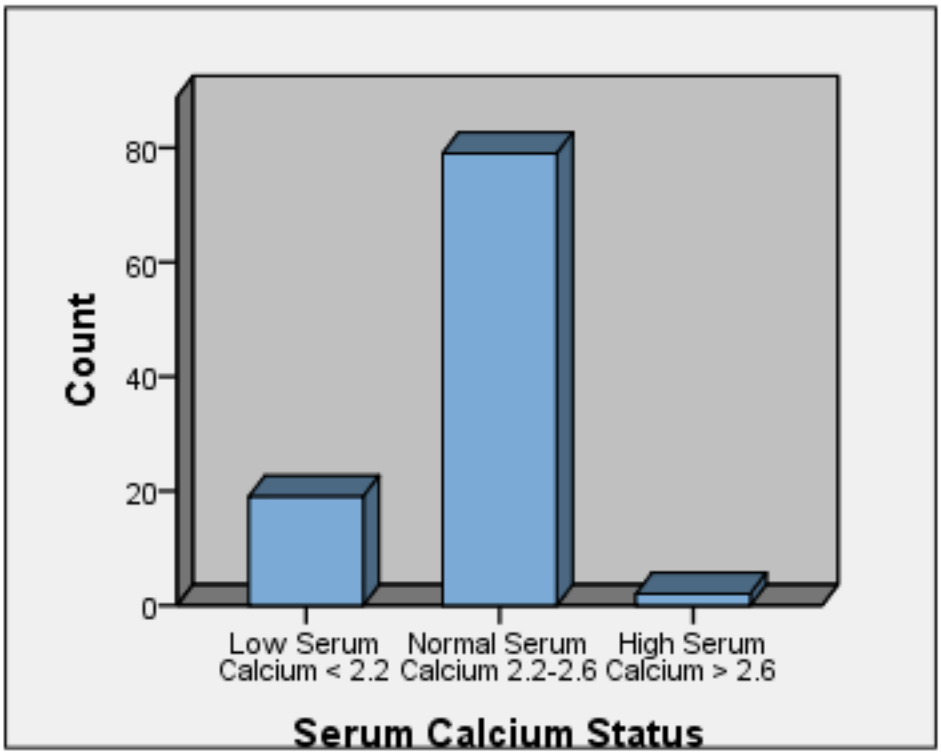

Figure 2: Serum Calcium status of thalassemic patients

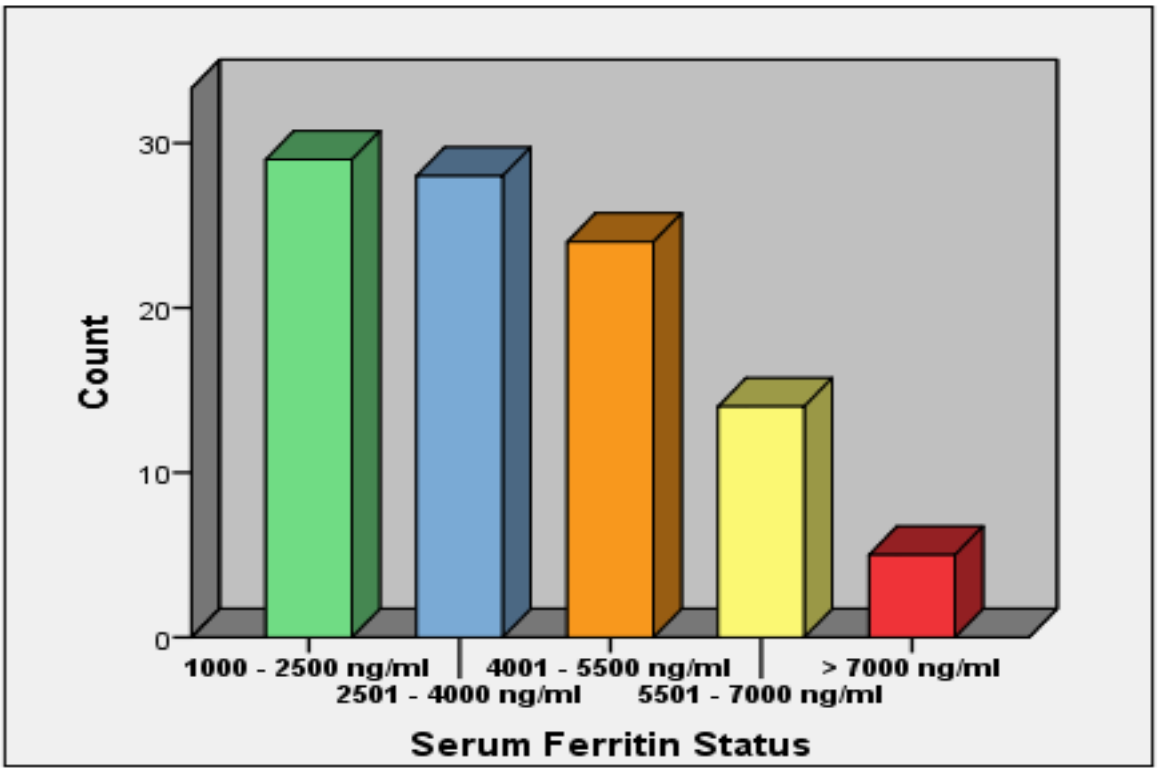

Figure 3: Range of serum ferritin level (ng/ml) in thalassemic patients

No significant association was found between demographic variables (age, gender,) and clinical variables (age of onset and frequency of blood transfusion), and vitamin D deficiency (P-value > 0.05) while there is a significant association between the disease duration and vitamin D status. as shown in (Table 2).

Table 2: Distribution of demographic and clinical features of patients according to their vitamin D level

Variable		Vitamin D Status						P
		Deficient		Insufficient		Sufficient		
		No	%	No	%	No	%	
Age	Child ≤ 10 years	21	55.3	8	21.1	9	23.7	0.99
	Adolescent >10 years	35	56.5	13	21.0	14	22.6	
Gender	Male	18	52.9	8	23.5	8	23.5	0.88
	Female	38	57.6	13	19.7	15	22.7	
Duration of disease	≤ 5 years	1	12.5	1	12.5	6	75.0	0.001
	>5 years	55	59.8	20	21.7	17	18.5	
Frequency of blood	Each 2 weeks	47	58.0	14	17.3	20	24.7	0.37

transfusion	Each 3 weeks	5	41.7	5	41.7	2	16.7	
	Each 4 weeks	4	57.1	2	28.6	1	14.3	
Age of onset of transfusion	< 1 year	47	57.3	18	22.0	17	20.7	0.50
	≥ 1 year	9	50.0	3	16.7	6	33.3	

There is a significant association between serum ferritin, serum calcium, and vitamin D levels. The highest vitamin D deficiency percentage (100%) was noticed among; patients with high ferritin levels (5501-7000ng/ml), and low serum calcium levels (< 2.2mmol/l) as shown in (Table 3).

Table 3: Relation between Vitamin D status and Serum ferritin and Serum calcium

Variable		Vitamin D status						P value
		Deficient		Insufficient		Sufficient		
		No	%	No	%	No	%	
Serum Ferritin Status	1000-2500	2	6.9%	9	31.0%	18	62.1%	<0.001
	2501-4000	14	50.0%	10	35.7%	4	14.3%	
	4001-5500	22	91.7%	1	4.2%	1	4.2%	
	5501-7000	14	100.0%	0	0.0%	0	0.0%	
	>7000	4	80.0%	1	20.0%	0	0.0%	
Serum Calcium Status	Low serum calcium < 2.2	19	100.0%	0	0.0%	0	0.0%	<0.001
	Normal serum calcium 2.2-2.6	37	46.8%	21	26.6%	21	26.6%	
	High serum calcium > 2.6	0	0.0%	0	0.0%	2	100.0%	

Most patients complaining of vitamin D deficiency had high serum ferritin levels, and nearly all patients with ferritin levels exceeding 5500 ng/ml complained of vitamin D deficiency or insufficiency as shown in (Figure 4).

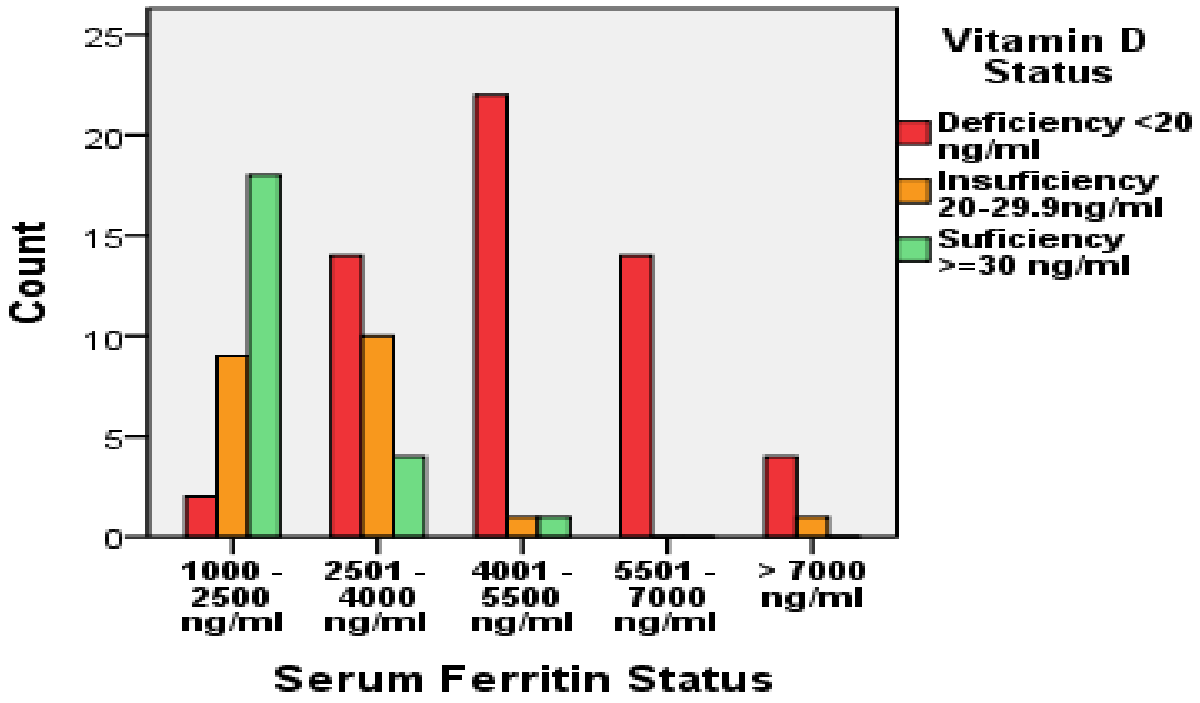

Figure 4: Vitamin D status among different serum ferritin levels

4. Discussion

This study revealed a significant prevalence (77%) of Vitamin D deficiency and insufficiency in multi-transfused thalassemia patients. The mean 25-OH Vit D levels of our study patients was 24.94±14.66 ng/ml. Vitamin D deficiency and insufficiency are reported to be high in thalassemic patients in many countries despite the presence of good sunshine and routine prescriptions. This agrees with; Merchant et al. who found vitamin D deficiency in 62% of Indian thalassemia major children (21), and Gombar et al. who found that the level of serum vitamin D was significantly low (*P* value < 0.0001) in thalassemic children (22), and Vogiatzi et al., who reported that 12% of thalassemic patients were vitamin D deficient and 69.8% had insufficient levels (23).

This shows that sun exposure alone is not sufficient to synthesize vitamin D in children with thalassemia (24)

The mean total serum Ca concentration was 2.28±0.18 mmol/l which is considered within the normal range, and only 19% had low serum calcium levels, this result goes with a survey conducted in Doha, Qatar revealed that 5% of thalassemia patients had low serum calcium levels (25), and was against Eren E et al (26), Autio et al (27), and Tantawy et al found that 75% of their study patients had low levels of serum calcium (28),

The mean serum ferritin level was 3940.48 ± 2287.76 ng/ml, which is markedly higher than the normal recommended levels for normal individuals. Normal values of serum ferritin for men and women are 12-300 ng/mL and 12-150 ng/mL, respectively (29). None of the study patients had a normal serum ferritin level, this iron overload that occurs as an unavoidable complication as a consequence of an excessive number of blood transfusions can result in a number of diseases and complications and may occur due to poor chelation treatment (30,31). This goes with Rashid Merchant et al., who found that all children had high serum ferritin levels (32).

When the association between vitamin D and frequency of blood transfusion, and the age of onset of transfusion were compared, it was non-significant. This can be explained by other factors that play a role in the regulation of vitamin D levels, this was in accordance with the study done by Hadeer AA et al which stated that vitamin D deficiency in thalassemic patients may caused by

many factors like decreased intake, defective skin synthesis, impaired absorption (33).

Our study also goes with RK Marwaha et al, Akhouri MR et al, and Seema P et al, who found that vitamin D deficiency occurs in patients with iron overload (34,35,36).

5. Conclusion

Vitamin D deficiency and insufficiency are common in thalassemia major patients possibly due to iron overload and poor nutritional support. This may be the cause of decreased bone mineral accretion and growth failure. So, frequent monitoring of 25 hydroxy Vitamin D levels in these patients for early detection and timely interventions whether preventive or therapeutic for correction of Vitamin D to prevent severe complications is recommended.

Also, the high level of serum ferritin in transfusion-dependent beta-thalassemia major patients noted in this study supports the importance of regular follow-up of those patients with respect to iron overload to ensure proper management of iron overload-associated complications. Proper chelation of iron overload could improve the quality of life of those patients.

6. References

[1]. NR Thiagarajan, Cg Delhi Kumar, Jayaprakash Sahoo, And Sriram Krishnamurthy. Effect of Vitamin D and Calcium Supplementation on Bone Mineral Content in Children with Thalassemia.Indian Pediatrics VOLUME 56: APRIL 15, 2019.

[2]. Windiastuti E, Nency YM, Mulatsih S, Sudarmanto B, Ugrrasena I. Buku Ajar Hematologi Onkologi Anak. In Jakarta: Badan Penerbit Ikatan Dokter Indonesia; 2018.

[3]. Kesse-Adu R, Howard J. Inherited anemias: sickle cell and thalassemia. Medicine. 2013;41(4):219–24.

[4]. Hoffman R, Jr EJB, Silberstein LE, Helsop HE, Weitz JI, Anastasia J, et al. Hematology Basic Principles and Practice 7th Edition. In: 7th Editio. Philadelphia: Elsevier; 2018. p. 546–70. Available from: https://linkinghub.elsevier.com/retrieve/pii/C20130233559.

[5]. Sevindik M. 2019. The novel biological tests on various extracts of Cerioporus varius. Fresenius Environmental Bulletin. 28(5): 3713-3717.

[6]. Salama OS, Al-Tonbary YA, Shahin RA, Eldeen OA. Unbalanced bone turnover in children with β-thalassemia, hematology, 2006,11(3),197-202. [PubMed]

[7]. Makki H., M.M., Asseel K., Al-Saad R., AL-Dujaili W., Relationship of levels of transforming growth factorbeta1 (TGF-β1) to the levels of ferritin in blood of transfusion dependent β-thalassemia major patients with growth retardation: A case-control study. EurAsian Journal of BioSciences, 2020. 14: 7, 521-527.

[8]. Muncie HL, Campbell JS. Alpha and Beta Thalassemia. Am Fam Physician. 2009;80(4):339–44.

[9]. Shah FT, Sayani F, Trompeter S, Drasar E, Piga A. Challenges of blood transfusions in beta-thalassemia. Blood Rev. (2019) 37:100588. doi: 10.1016/j.blre.2019.100588.

[10]. Kadhim KA, Baldawi KH, Lami FH. Prevalence, incidence, trend, and complications of thalassemia in Iraq. Hemoglobin. 2017;41(3):164-168

[11]. S.M. Jeon, E.A. Shin, Exploring vitamin D metabolism and function in cancer. Experimental and Molecular Medicine, 50 (2018). 20. doi:10.1038/s12276-018-0038-9.

[12]. Xu Z, Fan C, Zhao X, Tao H (2016) Treatment of osteoporosis with eldecalcitol, a new vitamin D analog: a comprehensive review and meta-analysis of randomized clinical trials. Drug Des Devel Ther 10:509–517.

[13]. 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. Pediatr Rev Int J Pediatr Res. 2016;3(09).

[14]. Chatterjee R, Bajoria R (2009) Osteopenia–osteoporosis syndrome in patients with thalassemia: understanding of type of bone disease and response to treatment. Hemoglobin 33(1):136–S138.

[15]. Voskaridou E, Terpos E. New insights into the pathophysiology and management of osteoporosis in patients with beta thalassemia. Br J Haematol. 2004;127:127–39. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]

[16]. S. Gombar, K. Parihar, M. Choudhary, S. Gombar, J.R. Med, S. Feb, Comparative study of serum ferritin and vitamin D in thalassemia patients with healthy controls. Int J Res Med Sci 6 (2018) 693-695

[17]. A. Soliman, V. De Sanctis, M. Yassin, Vitamin D Status in Thalassemia Major : an Update. Mediterr J Hematol Infect Dis. 2013; 5(1): e2013057. https://doi.org/10.4084/mjhid.2013.057.

[18]. Antonenko O, Bryk G, Brito G, Pellegrini G, Zeni S. Oral health in young women having a low calcium and vitamin D nutritional status. Clin Oral Invest. 2015;19(6):1199–206.

[19]. Calcium metabolism in health and disease. Peacock M. *Clin J Am Soc Nephrol.* 2010;5:0–30. [PubMed] [Google Scholar].

[20]. Cappellini MD, Cohen A, Porter J, Taher A, and Viprakasit V Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT). 3rd ed. Nicosia, Cyprus: Thalassaemia International Federation; 2014. [Google Scholar]

[21]. Merchant R, Udani A, Puri V, D'cruz V, Patkar D, Karkera A (2010) Evaluation of osteopathy in thalassemia by bone mineral densitometry and biochemical indices. The Indian Journal of Pediatrics 77(9):987–991. https://doi.org/10.1007/s12098-010-0158-2.

[22]. Gombar S, Parihar K, Choudhary M (2018) Comparative study of serum ferritin and vitamin D in thalassemia patients with healthy controls. Int J Res Med Sci 6(2):693–695. https://doi.org/10.18203/2320-6012.ijrms20180322.

[23]. 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 thalassemia 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

[24]. 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;17(5):291–6

[25]. A. Soliman, A. Adel, M. Wagdy, M. Al Ali, and N. ElMulla, 'Calcium Homeostasis in 40 Adolescents with Be-ta Thalassemia Major: A Case-Control Study of the Effects of Intramuscular Injection of a Megadose of Cholecalciferol', Pediatric Endocrinology Reviews, 6 Suppl 1 (2008), 149-54

[26]. Eren E, Yilmaz N. Biochemical markers of bone turnover and bone mineral density in patients with B thalassemia major. Int J Clin Pract. 2005;59(1):46–51. [PubMed]

[27]. 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

[28]. A. A. Tantawy, M. El Kholy, T. Moustafa, and H. H. Elsedfy, 'Bone Mineral Density and Calcium Metabolism in Adolescents with Beta-Thalassemia Major', Pediatric Endocrinology Reviews, 6 Suppl 1 (2008), 132-5.

[29]. Berdoukas V, Farmaki K, Carson S, et al. Treating thalassemia major-related iron overload: the role of deferiprone. J Blood Med. 2012;3:119–29. [PMC free article] [PubMed] [Google Scholar]

[30]. Riaz H, Riaz T, Khan MU, et al. Serum ferritin levels, socio-demographic factors and desferrioxamine therapy in multi-transfused thalassemia major patients at a government tertiary care hospital of Karachi, Pakistan. BMC research notes. 2011;4:287–287. [PMC free article] [PubMed] [Google Scholar]

[31]. Knovich MA, Storey JA, Coffman LG, et al. Ferritin for the clinician. Blood Rev. 2009;23:95–104. [PMC free article] [PubMed] [Google Scholar]

[32]. 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.

[33]. Abbassy H, Abo Elwafa R, Omar O (2019) Bone Mineral Density And Vitamin D Receptor Genetic Variants In Egyptian Children with Beta Thalassemia On Vitamin D Supplementation. Mediterranean Journal Of Hematology And Infectious Disease 11.

[34]. Marwaha R, Tandon N, Reddy D, Aggarwal R, Singh R, et al. (2015) Vitamin D and bone mineral density status of healthy schoolchildren in northern India. The American Journal of Clinical Nutrition 82:477-82.

[35]. Akhouri MR, Neha D (2017) Assessment of Vitamin D Status and Growth Parameters in Thalassemia Major Patients. IOSR-JDMS 16: 57-60.

[36]. Puri S,Marwaha R, Agarwal N,Tandon N, Agarwal R, et al. (2007) Vitamin D status of apparently healthy schoolgirls from two different socioeconomic strata in Delhi: relation to nutrition and lifestyle. British Journal of Nutrition 99: 876-82.

[37]. Aljalaly, S. A. S., Said, A. A. (2023). The Role of Vitamin C and Salt Stress and their Interactions in Some Characteristics of Wheat Yield. *Journal of Global Scientific Research*. 8(3): 3014-3019.