ASSESSMENT OF VITAMIN D AND CALCIUM LEVELS IN MULTI TRANSFUSED ß-THALASSEMIA SYNDROME PATIENTS OF DISTRICT PESHAWAR

Tariq Hamayun[1], Nazish Farooq*[1], Tariq Masood[1]

[1] Department of Haematology, Institute of Basic Medical Sciences, Peshawar, Pakistan
Address for correspondence:
Nazish Farooq
Assistant Professor
Department of Haematology, Institute of Basic Medical Sciences, Peshawar, Pakistan
E-mail: nazish.shinwari@yahoo.com

ABSTRACT

Background: Thalassemia syndrome represents a heterogeneous group of inherited anemias. It is one of the most common hereditary genetic disorders in Pakistan. Vita-min D is an important metabolite known to be deranged in various systemic illnesses involving kidneys, liver, GIT and endocrine system. Defective synthesis of 25-OH vi-tamin D have been described in these patients which negatively affect their bone metabolism. Impaired calcium homeostasis is thought to be a consequence of iron overload seen in multi-transfused thalassemia patients. Objective of the study was to assess serum vitamin D and calcium levels in ß thalassemia syndrome patients of district Peshawar.

Methodology: The current study had descriptive study design with cross-sectional time prospect. A total of 141 thalassemia syndrome patients were enrolled in the study. Physical examination was performed followed by collection of blood sam-ples. The samples were then processed and analyzed in the laboratories of Insti-tute of Basic Medical Sciences, Khyber Medical University, Peshawar.

Results: The mean age of our study group patients was 12.62+5.10 years. The mean 25-OH Vit D levels were 17.48+11.34 ng/dl, while mean total serum Ca con-centration was 8.67+9.1 mg/dl. Only 21.3% of our patients had optimal/normal levels of serum vitamin D concentration. 72.3% of our study patients had normal levels of their total serum calcium, while 27% of patients had low total serum calcium levels and 0.7% had high levels for serum calcium.

Conclusion: The present study showed a high prevalence of VDD and low total serum calcium levels in thalassemia patients with a significant low BMI, that signify the importance of screening for said metabolites and appropriate ther-apeutic interventions. The presence of such metabolic derangements may be due to the presence of high serum ferritin levels and poor nutrition intake. Appropriate measurements therefore should be taken to improve heath and quality of life in thalassemia patients.

Keywords: Thalassemia syndrome, 25-OH Vitamin D, Calcium, Body mass index (BMI)

This article may be cited as: Hamayun T, Farooq N, Masood T. Assessment of vitamin d and calcium levels in multi transfused ß thalassemia syndrome patients of district peshawar. Adv Basic Med Sci. 2017;1(2): 41-47.

INTRODUCTION

Thalassemia syndrome represents a heterogeneous group of inherited anemias signified by defective synthesis of one or more globin chain subunits of haemoglobin (Hb) tetramer. Thalassemia are autosomal recessive disorders. There are several types of thalassemia with clinical picture ranging from barely detectable hematological abnormality to severe and fatal anemia[20]. The defect primarily is quantitative i.e. reduced or absent synthesis of the normal globin chains, but there are mu-tations as well which result in structural variants pro-duced at reduced rate (e.g. HbE, Hb Lepore). This re-sults in reduced hemoglobin in red blood cells (RBCs) as well as decreased production of RBCs that consequently leads to anemia.

Vitamin D is essential for calcium homeostasis and for mineralization of skeleton, especially during periods of rapid growth like infantile and pubertal growth peri-ods. Vitamin D deficiency (VDD) can lead to rickets (a mineralization defect at the epiphyseal growth plates and bone tissue) and osteomalacia (a mineralization defect of bone tissue)[21]. In thalassemia patients, bone disease becomes an important cause of morbidity that includes rickets, osteoporosis, spinal deformities, scoli-osis, fractures and nerve compression[23,36,37].

Vitamin D is an important metabolite known to be de-ranged in various systemic illnesses involving kidneys[22], liver[27], gastro intestinal tract (GIT)[21] and endocrine sys-tem[21]. Impaired calcium homeostasis is thought to be a consequence of iron overload seen in multi-transfused thalassemia patients. Defective synthesis of 25 OH vi-tamin D have been described in these patients which negatively affect their bone metabolism[3,18,23]. Haemato-logical disorders like thalassemia syndrome used to be a potential lethal disease previously, but advancement in therapies and optimized transfusion programs have improved quality and life expectancy of these patients.

Thalassemia is one of the most common hereditary genetic disorders in Pakistan with a very high region-al and geographical prevalence[19]. Owing to the limited sources in local set-up, thalassemia major patients un-dergo frequent transfusions without proper monitoring which make them prone to develop complications in the said bodily systems chiefly due to iron overload[2]. A study depicting description of vitamin D levels in local thal-assemia major population is lacking. The current study will bring forth primary details which will guide further research in this regard.

METHODOLGY

The study was commenced after approval from Ad-vanced Studies & Research Board (ASRB) and Ethical Re-search Committee, KMU. It was conducted from June 2014 to December 2014. Eligible patients were identi-fied and contacted at transfusion centers and thalas-semia day care clinics of major teaching hospitals. Prop-er NOCs were obtained from these centers. Purpose and benefits of the study were explained to the patients and informed written consent was taken.

Patients from district Peshawar with ß thalassemia syndrome, who were pre-diagnosed with ß thalassemia syndrome based on electrophoresis testing, were in-cluded in the study. Patients taking vitamin D and cal-cium supplements were excluded from the study. Also patients with any other systemic co-morbidity and/or other chronic hemolytic anemia were not enrolled.

To measure serum vitamin D levels, Euro-Immune® 25-OH Vitamin D kit was used. The kit employs an ELISA (enzyme-linked immunosorbent assay) based technique called competitive ELISA on Rayto® microplate reader. Serum Calcium levels were measured using Calcium Ar-senazo® kit on Microlab 200®. Optimal level of vitamin D is defined as 25-OH Vit D concentration greater than 30 ng/ml, mild to moderate VDD is defined levels of 25-OH Vit D from 10-30 ng/ml, while sever deficiency is categorized as concentration of 25-OH Vit D less than 10 ng/ml.

Statistical Package for Social Sciences (SPSS) pro-gram (version 20) was used to statistically evaluate the study findings. Student t-test was posed to find similar-ity/difference among groups. Significance level was set at p-value of 0.05.

RESULTS

Clinical and Demographic Data

A total of 141 thalassemia syndrome patients were recruited for current study (Table 1), including 78 male and 63 female patients; 119 patients were from pediat-ric age group (< 18 years) and 22 were from adult group (18 years and above). The mean age of our study group patients was 12.62+5.10 years.

Table 1 Gender-Age description of study group

	Age Group		Total
	Pediatric Group	Adult Group	
Males	66	12	78
Females	53	10	63
Total	119	22	141

BIOCHEMICAL STUDIES

In our study we found that the mean 25-OH Vit D levels of our study patients was 17.48±11.34 ng/dl, while mean total serum Ca concentration was 8.67±9.1 mg/ dl. Only 21.3% of our patients had optimal/normal levels of serum vitamin D concentration, while 46.1% had mild to moderate deficiency and 32.6% were absolute/ severe deficient in serum 25-OH Vit D concentration. Of all, 27% of patients had low total serum calcium level while 72.3% had normal and 0.7% had high levels of their total serum calcium levels. Mean serum ferritin level

Table 2 Serum ferritin levels of study patients

		Frequency	Percentage (%)	Cumulative Percentage
Serum Ferritin	Mildly Raised	2	1.4	1.6
	Moderately Raised	35	24.8	28.5
	Severely Raised	61	43.3	49.6
	Very Severely Raised	25	17.7	20.3
	Total	123	87.2	100.0
	Missing	18	12.8	
Total		141	100.0	

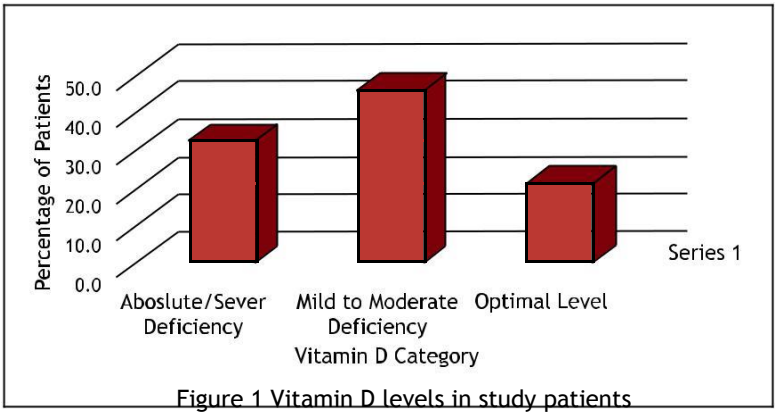

Figure 1 Vitamin D levels in study patients

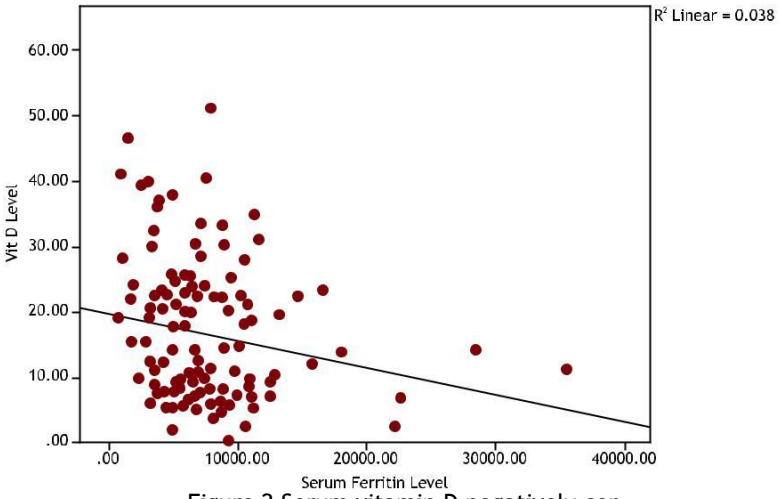

Figure 2 Serum vitamin D negatively correlates with serum ferritin levels

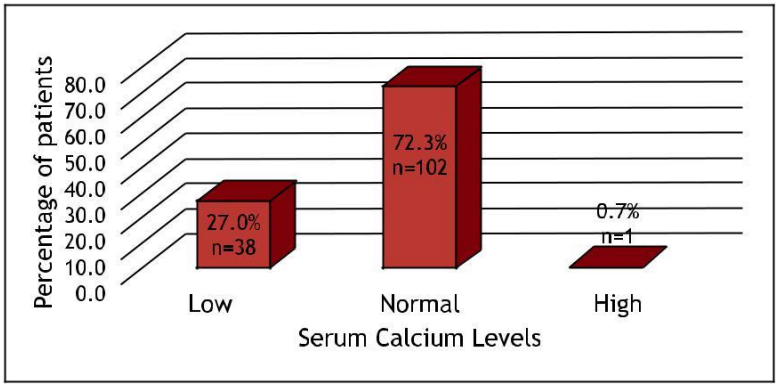

Figure 3 Serum total calcium levels of study patients

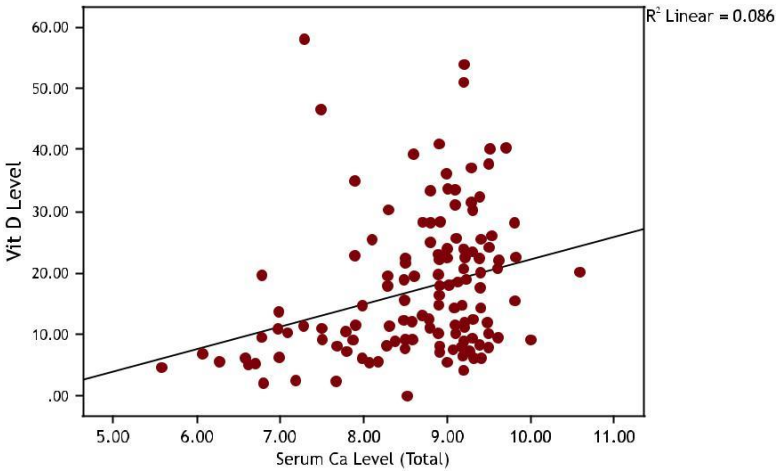

Figure 4 Strong positive association between serum vitamin D and serum calcium levels

was 7555±5029 ng/ml. None of the study patients had normal serum ferritin level (Table 2).

DISCUSSION

Our study revealed a significant prevalence (78.7%) of VDD in multi-transfused thalassemia syndrome pa-tients of district Peshawar (Figure 1). A study conducted in North America reported VDD in 82% of study patients, with serum vitamin D levels less than 30 ng/ml[26]. Stud-ies from Asia revealed prevalence of VDD among thalas-semia patients ranging from 37% to 100%[28,30]. Prevalence of VDD in thalassemia patients from Europe has been found to vary considerably, ranging from 36% to 87%[6,35]. Similarly, a survey conducted in September 2012 on thalassemia patients from Africa reported a VDD preva-lence of 91% in thalassemia patients[13].

A trend could not be established in studies from dif-ferent thalassemia populations from around the world. Our study patients share ranks with the highest VDD prevalence regions.

Studies have shown an almost similar prevalence rate of VDD in thalassemia population when compared to normal population; the mean serum vitamin D, however, is found to have been significantly lower in thalassemia population[13,25]. A local cross sectional survey in asymp-tomatic normal population comprised of 300 individu-als, reported VDD in 84.3% of subjects with a median value of 18.8 ng/dl[29]. This prevalence is close what we found in our study patients, however, the median vita-min D value in our study group was significantly lower (i.e. 14.5 ng/dl).

A significant negative correlation (p value 0.030) of serum vitamin D & serum ferritin concentration was found in the current study (Figure 2).

Negative correlation between ferritin and 25-OHD is found in several other ethnicities as well[12,25]. It is already known that high serum ferritin levels are associated with increased liver iron concentration[24,33]. Iron deposition in turn, impairs liver metabolism of 25-OHD, thus lowering vitamin D level in the body[8-10,25].

Calcium levels were found to have been low in 27% of the study patients (Figure 3). A study from Turkey in 2012 reported that 27.66% thalassemia patients had low serum calcium levels[4]. Tantawy et al found that 75% of their study patients had low levels of serum calcium levels[34]. Another survey conducted at Doha, Qatar revealed that 5% of thalassemia patients had low serum calcium levels[31]. A study conducted in India in 2008 showed a mean level of 5.534±1.11 mg/dl[5]N</author><author>Khalida Parveen</author><author>Shetty, Beena</author><author>Shenoy, U. V.</author></authors></contributors><titles><title>Prevalence of Hypoparathyroidism (HPT. Fahim et al at Upper Egypt in 2013 found that mean total serum calcium level was 6.6+1.2mg/dl[13]. Our study findings are, thus in agreement to what has already been established earlier.

Vitamin D is primarily involved in calcium metabolism[1]. Serum 25-OHD levels less than 30 ng/dl is associated with a significant decline in intestinal calcium absorption[7,11,32]. Without vitamin D, only 10-15% of the dietary calcium is absorbed[14-16]. A positive correlation between serum calcium and vitamin D in thalassemia patients was found in a study by Zoga et al[17]. In our study we also found a significant positive correlation (p value < 0.001) between the two entities supporting the afore-mentioned concept (Figure 4).

Owing to lack of resources, the current study was limited to single (though largest and busiest) transfusion center from the region. High prevalence of VDD and low serum total calcium levels in our study emphasizes the importance of more detailed studies in thalassemia patients nationwide. It is recommended to monitor serum vitamin D and calcium levels routinely and commence appropriate therapy where necessary.

CONCLUSION

In the whole sum, our study revealed that 78.7% of local transfusion dependent ß-thalassemia patients are VDD whereas hypocalcemia prevails in 27% of these patients. It was also found that high serum ferritin levels are negatively associated with serum vitamin D levels. Low calcium levels were also found to have been positively correlated to low serum vitamin D levels. It is therefore advised to monitor these vital metabolites regularly and replenish where needed.

REFERENCES

1. Shaimaa K. Ali HA, 'Prevalence of Hypocalcemia among Thalassemic Patients Registred in Ibn Al-Balady Hospital (Thalassemic Centre) Baghdad Iraq', Tikrit Joumat of Phar-maceutical Sciences, 4(2):147'l5l (2008).

2. Syed Asad Ali, Rafe M. J. Donahue, Huma Qureshi, and Sten H. Vermund, 'Hepatitis B and Hepatitis C in Pakistan: Prevalence and Risk Factors', International Journal of In-fectious Diseases, 13 (2009), 9-19.

3. J. F. Aloia, J. A. Ostuni, J. K. Yeh, and E. C. Zaino, 'Com-bined Vitamin D Parathyroid Defect in Thalassemia Ma-jor', Arch Intern Med, 142 (1982), 831-2.

4. Ibrahim Aslan, Duran Canatan, Nihal Balta, Gulizar Kacar, Cengaver Dorak, Ahmet Ozsancak, Nurgul Oguz, and Ruya Cosan, 'Bone Mineral Density in Thalassemia Major Pa-tients from Antalya, Turkey', International Journal of En-docrinology, 2012 (2012), 4.

5. N Basha, Khalida Parveen, Beena Shetty, and U. V. Shenoy, 'Prevalence of Hypoparathyroidism (Hpt) in Beta Thalas-semia Major', Journal of Clinical and Diagnostic Research, 8 (2014), 24-26.

6. V. Benigno, S. Bertelloni, G. I. Baroncelli, L. Bertacca, S. Di Peri, L. Cuccia, Z. Borsellino, and M. C. Maggio, 'Effects of Thalassemia Major on Bone Mineral Density in Late Adolescence', J Pediatr Endocrinol Metab, 2 (2003), 337-42.

7. H. A. Bischoff-Ferrari, E. Giovannucci, W. C. Willett, T. Dietrich, and B. Dawson-Hughes, 'Estimation of Optimal Serum Concentrations of 25-Hydroxyvitamin D for Multiple Health Outcomes', Am J Clin Nutr, 84 (2006), 18-28.

8. M. Casale, S. Citarella, A. Filosa, E. De Michele, F. Palm-ieri, A. Ragozzino, G. Amendola, U. Pugliese, I. Tartagli-one, F. Della Rocca, P. Cinque, B. Nobili, and S. Perrotta, 'Endocrine Function and Bone Disease During Long-Term Chelation Therapy with Deferasirox in Patients with Be-ta-Thalassemia Major', Am J Hematol, 89 (2014), 1102-6.

9. L. H. Chow, J. V. Frei, A. B. Hodsman, and L. S. Valberg, 'Low Serum 25-Hydroxyvitamin D in Hereditary Hemochromatosis: Relation to Iron Status', Gastroenterology, 88 (1985), 865-9.

10. Soteroulla Christou, 'Vitamin D Levels Correlate with Iron Load and Glycemic Intolerance inThalassemia', Thalas-semia international fideration (2013).

11. H. F. DeLuca, 'Overview of General Physiologic Features and Functions of Vitamin D', Am J Clin Nutr, 80 (2004), 1689S-96S.

12. S. Domrongkitchaiporn, V. Sirikulchayanonta, P. Angchaisuksiri, W. Stitchantrakul, C. Kanokkantapong, and R. Rajatanavin, 'Abnormalities in Bone Mineral Density and Bone Histology in Thalassemia', J Bone Miner Res, 18 (2003), 1682-8.

13. Fahim M. Fahim, Khaled Saad, Eman A. Askar, Eman Nasr Eldin, and Ahmed F. Thabet, 'Growth Parameters and Vita-min D Status in Children with Thalassemia Major in Upper Egypt', International Journal of Hematology-Oncology and Stem Cell Research, 7 (2013), 10-14.

14. M. F. Holick, 'High Prevalence of Vitamin D Inadequacy and Implications for Health', Mayo Clinic Proceedings, 81 (2006), 353-73.

15. ———, 'Vitamin D Deficiency', The New England Journal of Medicine, 357 (2007), 266-81.

16. Michael F. Holick, 'The Vitamin D Epidemic and Its Health Consequences', The Journal of Nutrition, 135 (2005), 2739S-48S.

17. E.Refatllari J.Zoga, 'Level of Vitamin D in Patients Affected by ThalassemiaMajor and Sickle Cell Disease in the Center of Haemoglobinopathy Lushnja, Albania', EDIS - Publishing Institution of the University of Zilina ,, 3 (2014), 229-32.

18. M. Karimi, F. Habibzadeh, and V. De Sanctis, 'Hypoparathyroidism with Extensive Intracerebral Calcification in Patients with Beta-Thalassemia Major', J Pediatr Endocri-nol Metab, 16 (2003), 883-6.

19. S. N. Khan, and S. Riazuddin, 'Molecular Characterization of Beta-Thalassemia in Pakistan', Hemoglobin, 22 (1998), 333-45.

20. N. Koonrungsesomboon, S. C. Chattipakorn, S. Fucharoen, and N. Chattipakorn, 'Early Detection of Cardiac Involve-ment in Thalassemia: From Bench to Bedside Perspec-tive', World J Cardiol, 5 (2013), 270-9.

21. Elizabeth A. Krall, Nadine Sahyoun, Saul Tannenbaum, Gerard E. Dallal, and Bess Dawson-Hughes, 'Effect of Vitamin D Intake on Seasonal Variations in Parathyroid Hormone Secretion in Postmenopausal Women', New England Journal of Medicine, 321 (1989), 1777-83.

22. A. Levin, G. L. Bakris, M. Molitch, M. Smulders, J. Tian, L. A. Williams, and D. L. Andress, 'Prevalence of Abnormal Serum Vitamin D, Pth, Calcium, and Phosphorus in Patients with Chronic Kidney Disease: Results of the Study to Evaluate Early Kidney Disease', Kidney International, 71 (2006), 31-38.

23. P. Mahachoklertwattana, V. Sirikulchayanonta, A. Chuansumrit, P. Karnsombat, L. Choubtum, A. Sriphrapradang, S. Domrongkitchaiporn, R. Sirisriro, and R. Rajatanavin, 'Bone Histomorphometry in Children and Adolescents with Beta-Thalassemia Disease: Iron-Associated Focal Osteomalacia', J Clin Endocrinol Metab, 88 (2003), 3966-72.

24. Khaled M. Musallam, Maria Domenica Cappellini, John C. Wood, Irene Motta, Giovanna Graziadei, Hani Tamim, and Ali T. Taher, 'Elevated Liver Iron Concentration Is a Marker of Increased Morbidity in Patients with B Thalassemia Intermedia', Haematologica, 96 (2011), 1605-12.

25. N. Napoli, Enrico Carmina, Salvatore Bucchieri, C. Sferrazza, G. B. Rini, and G. Di Fede, 'Low Serum Levels of 25-Hydroxy Vitamin D in Adults Affected by Thalassemia Major or Intermedia', Bone, 38, 888-92.

26. O. Oliveros, F. Trachtenberg, D. Haines, E. Gerstenberger, M. Martin, S. Carson, S. Green, D. Calamaras, P. Hess, R. Yamashita, and E. Vichinsky, 'Pain over Time and Its Effects on Life in Thalassemia', Am J Hematol, 88 (2013), 939-43.

27. Salvatore Petta, Calogero Cammà, Concetta Scazzone, Claudio Tripodo, Vito Di Marco, Antonino Bono, Daniela Cabibi, Giusalba Licata, Rossana Porcasi, Giulio Marchesini, and Antonio Craxí, 'Low Vitamin D Serum Level Is Related to Severe Fibrosis and Low Responsiveness to Interferon-Based Therapy in Genotype 1 Chronic Hepatitis C', Hepatology, 51 (2010), 1158-67.

28. A. A. Shamshirsaz, M. R. Bekheirnia, M. Kamgar, N. Pourzahedgilani, N. Bouzari, M. Habibzadeh, R. Hashemi, S. Aghakhani, H. Homayoun, and B. Larijani, 'Metabolic and Endocrinologic Complications in Beta-Thalassemia Major: A Multicenter Study in Tehran', BMC Endocr Disord, 3 (2003), 4.

29. Adil Sheikh, Zeb Saeed, Syed Ali Danial Jafri, Iffat Yazdani,

and Syed Ather Hussain, 'Vitamin D Levels in Asymptomat-ic Adults-a Population Survey in Karachi, Pakistan', PLoS ONE, 7 (2012), e33452.

30. A. Soliman, A. Adel, M. Wagdy, M. Al Ali, and N. ElMulla, 'Calcium Homeostasis in 40 Adolescents with Beta-Thalassemia Major: A Case-Control Study of the Effects of Intramuscular Injection of a Megadose of Cholecalciferol', Pediatr Endocrinol Rev, 1 (2008), 149-54.

31. 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.

32. Ashraf Soliman, Vincenzo De Sanctis, and Mohamed Yassin, 'Vitamin D Status in Thalassemia Major: An Update', Mediterranean Journal of Hematology and Infectious Diseases, 5 (2013), e2013057.

33. T. G. St Pierre, P. R. Clark, W. Chua-anusorn, A. J. Fleming, G. P. Jeffrey, J. K. Olynyk, P. Pootrakul, E. Robins, and R. Lindeman, 'Noninvasive Measurement and Imaging of Liver Iron Concentrations Using Proton Magnetic Resonance', Blood, 105 (2005), 855-61.

34. A. A. Tantawy, M. El Kholy, T. Moustafa, and H. H. Elsedfy, 'Bone Mineral Density and Calcium Metabolism in Adoles-cents with Beta-Thalassemia Major', Pediatric Endocrinol-ogy Reviews, 6 Suppl 1 (2008), 132-5.

35. Ploutarchos Tzoulis, Ai Leen Ang, Farrukh T. Shah, Marko Berovic, Emma Prescott, Romilla Jones, and Maria Barnard, 'Prevalence of Low Bone Mass and Vitamin D Deficiency in B-Thalassemia Major', Hemoglobin, 38 (2014), 173-78.

36. B. Wonke, 'Bone Disease in Beta-Thalassaemia Major', Br J Haematol, 103 (1998), 897-901.

37. B. Wonke, C. Jensen, J. J. Hanslip, E. Prescott, M. Lalloz, M. Layton, S. Erten, S. Tuck, J. E. Agnew, K. Raja, K. Da-vies, and A. V. Hoffbrand, 'Genetic and Acquired Predis-posing Factors and Treatment of Osteoporosis in Thalas-saemia Major', J Pediatr Endocrinol Metab, 11 Suppl 3 (1998), 795-801.