ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

The Effects of Vitamin D on Myocardial Function Demonstrated by Speckle-Tracking Echocardiography in Children with Beta Thalassemia

Beta Talasemi ile Takipli Çocuk Hastalarda D Vitamininin Miyokard Fonksiyonları Üzerine Etkisinin Speckle Tracking Ekokardiyografi ile Değerlendirilmesi

ABSTRACT

Objective: Beta thalassemia major is an inherited hemoglobin disorder resulting in chronic hemolytic anemia. Cardiac involvement is the main cause of death in patients. Speckle-tracking echocardiography is a feasible method for the evaluation of cardiac function via an assessment of the longitudinal deformation of the myocardium through the cardiac cycle. The aim of our study is to evaluate the association between vitamin D deficiency and deformation of the left ventricular myocardium measured by speckle-tracking echocardiography in children with thalassemia major.

Yöntemler: In this prospective study, 33 thalassemic patients with vitamin D deficiency were enrolled. Cardiac magnetic resonance T2* value, conventional echocardiography, and speckle tracking, and also left ventricular longitudinal and circumferential strain values were measured. Myocardial functions of the patients with vitamin D deficiency or insufficiency were evaluated by speckle-tracking echocardiography before and after vitamin D replacement.

Results: The mean age of the patients was 15.4 ± 3.09 years. Vitamin D level was deficient in 30 (90%) and insufficient in 3 (10%) of them. Speckle-tracking analysis showed a significantly decreased absolute value of the left ventricular global longitudinal strain before vitamin D replacement. A significant improvement in the global longitudinal strain was detected after vitamin D replacement ($P < 0.05$). A statistically significant increase was observed in parameters showing left ventricular systolic and diastolic functions after vitamin D replacement.

Conclusion: Vitamin D deficiency is frequently observed and causes decreased contractility in thalassemic patients. In our study, we observed that our patients' cardiac functions had improved after vitamin D replacement therapy.

Keywords: Cardiac function, thalassemia major, vitamin D

ÖZET

Amaç: β-talasemi major, kronik hemolitik anemi ile sonuçlanan kalıtsal bir hemoglobinopatidir. Kardiyak komplikasyonlar hastalarda başlıca ölüm nedenidir. Speckle-tracking ekokardiyografi, kalp döngüsü boyunca miyokardın longitudinal deformasyonunun değerlendirilmesi yoluyla kalp fonksiyonunun değerlendirilmesi için uygun bir yöntemdir. Çalışmamızın amacı talasemi major nedeni ile takipli çocuk hastalarda vitamin D eksikliğinin sol ventrikül fonksiyonlarına olan etkilerinin speckle-tracking ekokardiyografi yöntemi ile değerlendirilmesidir.

Metod: Bu prospektif çalışmaya vitamin D eksikliği olan 33 talasemi major hastası dahil edildi. Hastaların kardiyak T2* manyetik rezonans görüntülemeleri, konvansiyonel ekokardiyografileri ve speckle-tracking ekokardiyografi ile sol ventrikül fonksiyonları analiz edildi. Vitamin D eksikliği veya yetersizliği olan hastaların miyokardiyal fonksiyonları, vitamin D replasmanı öncesi ve sonrasında speckle-tracking ekokardiyografi yöntemi ile değerlendirildi.

Bulgular: Hastaların yaş ortalaması 15,4 ± 3,09 yıl idi. Vitamin D düzeyi; hastalarımızın 30'unda (%90) eksik, 3'ünde ise (%10) yetersizdi. Speckle tracking ekokardiyografide, sol ventrikül global longitüdinal strain değerinin vitamin D replasmanı öncesinde belirgin düşük olduğu görüldü. Vitamin D replasmanı sonrasında sol ventrikülün global longitüdinal strain değerinde anlamlı iyileşme olduğu gözlendi ($P < 0,05$). Vitamin D replasmanı sonrasında, sol ventrikül sistolik ve diyastolik fonksiyonlarını gösteren parametrelerde istatistiksel olarak anlamlı artış görüldü.

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

Ayça Koca Yozgat[1]
Emine Azak[2]
Dilek Kaçar[1]
Melek Işık[1]
Özlem Arman Bilir[1]
Zeliha Güzelküçük[1]
İbrahim İlker Çetin[3]
Namık Yaşar Özbek[1]
Neşe Yaralı[4]

[1]*Department of Pediatric Hematology-Oncology, Ankara Health Sciences University, Ankara City Hospital, Ankara, Türkiye*
[2]*Department of Pediatric Cardiology, Ankara Health Sciences University, Ankara City Hospital, Ankara, Türkiye*
[3]*Department of Pediatric Cardiology, Yıldırım Beyazıt University, Ankara City Hospital, Ankara, Türkiye*
[4]*Department of Pediatric Hematology-Oncology, Yıldırım Beyazıt University, Ankara City Hospital, Ankara, Türkiye*

Corresponding author:
Ayça Koca Yozgat
✉ draycayozgat@yahoo.com

Received: October 24, 2022
Accepted: January 30, 2023

Cite this article as: Koca Yozgat A, Azak E, Kaçar D, 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):328-332.

DOI:10.5543/tkda.2023.85265

Sonuç: Vitamin D eksikliği talasemi major nedeni ile takipli hastalarda sıklıkla görülmekte olup, kardiyak kontraktilitede azalmaya neden olabilmektedir. Çalışmamızda, vitamin D replasman tedavisi sonrası hastalarımızın kardiyak fonksiyonlarının düzeldiğini gözlemledik.

Anahtar Kelimeler: Kardiyak fonksiyonlar, talasemi major, vitamin D

Beta thalassemia major (β-TM) is an autosomal recessive disorder caused by the homozygous deletion of the β-globin chain gene and characterized by microcytic hypochromic anemia.[1] Frequent erythrocyte transfusion and iron chelation therapy are the mainstays of the treatment. Despite significant improvements in the treatment -due to frequent blood transfusions- patients are susceptible to excess iron deposition in vital organs like the heart, liver, and endocrine glands.[2] Although iron-chelating agents have vastly improved prognosis, iron overload may initiate structural changes in the myocardium that can eventually lead to heart failure, which is considered the major cause of death in thalassemic patients.[3]

Vitamin D deficiency is common in patients with β-TM due to decreased outdoor activities and limited sun exposure, genetic and cultural factors, or dark skin. Furthermore, vitamin D deficiency may be due to decreased synthesis of 25-hydroxy-vitamin D (25-OH vitamin D) as a result of iron accumulation in the liver.

Epidemiologic studies have shown that vitamin D deficiency was associated with chronic diseases such as cancer, diabetes, autoimmune diseases, and cardiovascular disease (hypertension, coronary artery disease, peripheral artery disease, heart failure, and stroke).[4] Vitamin D deficiency leads to an increase in serum parathyroid hormone (PTH). The PTH affects the myocardium directly through downstream actions of G-protein-coupled receptors and is associated with a decrease in cardiac function, muscle weakness, and left ventricular hypertrophy.[5,6] Also, vitamin D can affect cardiac function by regulating the renin -angiotensin-aldosterone system and regulating blood pressure effects. Activated vitamin D suppresses renin gene expression in vitro and regulates the growth and proliferation of vascular smooth muscle cells and cardiomyocytes.[7]

In thalassemic patients, conventional echocardiography that examines ejection fraction and fractional shortening is not exactly adequate for early diagnosis of cardiac iron overload and subclinical cardiac systolic dysfunction.[8] Speckle-tracking echocardiography (STE) is a relatively more sensitive echocardiographic modality and appears to be capable of providing a useful regional functional assessment of myocardial segments via an assessment of the longitudinal deformation of the myocardium through the cardiac cycle. Speckle-tracking echocardiography can assess regional and/or globally subtle left ventricular (LV) myocardial impairment with strain and strain rate measurements.[9]

This study aimed to evaluate myocardial function using STE in children with thalassemia major and no obvious heart disease before and after vitamin D treatment.

ABBREVIATIONS

β-TM	Beta thalassemia major
PTH	Parathyroid hormone
STE	Speckle-tracking echocardiography
LVEF	Left ventricular ejection fraction
LVSF	Left ventricular shortening fraction
LVGLS	Left ventricular global longitudinal strain
LVGCS	Left ventricular regional global circumferential strain
RVGLS	Right ventricular global longitudinal strain

Materials and Methods

Study Population

This prospective study enrolled 33 patients with transfusion-dependent thalassemia who were followed at Pediatric Hematology-Oncology Department from April 2018 to January 2020. Inclusion criteria were (1) transfusion-dependent β-TM major with regular monthly transfusions, (2) age between 5 and 25 years, (3) no active liver or kidney disease, (4) serum $25\text{-}OHD_3 < 30$ ng/mL, and (5) no history of vitamin D injection in the preceding 6 months. Exclusion criteria were the presence of congenital heart disease, liver disease, kidney disease, and type 1 diabetes. Data including gender, age, hemoglobin levels, ferritin levels, and chelation therapy type were obtained from medical records. Calcium, phosphate, alkaline phosphatase, PTH, and vitamin D levels were measured.

Clinical Data

Cardiac function, left ventricular ejection fraction (LVEF), and left ventricular shortening fraction (LVSF) were evaluated by conventional echocardiography. A commercially available ultrasound system (iE33, Philips, Eindhoven, The Netherlands), equipped with a broadband (1-5 MHz) S5 transducer was used to obtain 2D grayscale harmonic images at a frame rate of 60-80 frames per second (frames/s). Two-dimensional and M-mode echocardiography were used to measure left ventricular end-diastolic and end-systolic diameter, end-diastolic septal and posterior wall thickness, EF, and shortening fraction (FS), according to the guidelines of the American Society of Echocardiography.[10]

All 2-dimensional STE analyses were performed by the same investigator to avoid inter-observer variability. Myocardial deformation parameters (S and SR) were measured using commercially available software (QLAB Advanced Quantification Software, version 6.0, TMQ, Philips Medical Systems, Best, Eindhoven, The Netherlands) on standard 2D grayscale LV images from the standard apical 4-chamber view (AP4) for longitudinal strain and standard parasternal short axis at the papillary muscle level (PML) for circumferential strain. Two consecutive beats synchronized to continuous electrocardiography (ECG) were recorded with a frame rate set to >60 frames/s. The data were transferred to the QLAB software system for offline analysis. The endocardial borders were identified manually to include the entire myocardium in all view areas. The following peak systolic LV and RV STE parameters were measured:

- LVGLS: Left ventricular global longitudinal strain at AP4,
- LVGLSR: Left ventricular global longitudinal strain rate at AP4,
- LVGCS: Left ventricular global circumferential strain at PML,
- LVGCSR: Left ventricular global circumferential strain rate at PML,
- RVGLS: Right ventricular global longitudinal strain at AP4,
- RVGLSR: Right ventricular global longitudinal strain rate at AP4.

Cardiac iron was determined by cardiac T2* magnetic resonance imaging. Cardiac iron overload was defined as cardiac T2∗ ≤20 ms. Vitamin D level < 20 ng/mL indicated deficiency; 20-30 ng/mL indicated insufficient, and >30 ng/mL indicated sufficient. A PTH level > 65 pg/mL indicated hyperparathyroidism. Vitamin D replacement was given to patients who are vitamin D deficient or insufficient and it was observed that vitamin D levels came to normal. Myocardial functions of patients with vitamin D deficiency or insufficiency were evaluated by conventional echocardiography and STE before and after vitamin D replacement. The patients' erythrocyte transfusion period was every 3-4 weeks. The patients' echocardiography and STE were performed after the transfusion of the patients so that the anemia was not affected by the parameters.

The study protocol was reviewed and approved by the Ethics Committee of our hospital. Assent and informed consent were obtained from all participants and their parents or legal guardians.

Statistical Analysis

Statistical Package for Social Sciences for Windows (version 18; SPSS Inc., Chicago, Ill, USA) was used for the statistical analysis. The Kolmogorov-Smirnov test was used to analyze the distribution of continuous variables. Numeric variables are expressed as the mean ± SD and median. Chi-square analysis was used to compare continuous and categorical variables between groups. Comparisons of demographic data and echocardiographic parameters between patients and controls were performed using the Mann–Whitney *U*-test for non-normally distributed variables. Spearman's correlation coefficient was used to disclose possible correlations between vitamin D levels and all echocardiographic data. A difference was considered statistically significant at a *P*-value of <0.05.

Results

The study included 33 patients (18 male/15 female); the mean age was 15.4 ± 3.09 years. The mean heart rate of the patients was 96 ± 14 beats/min. The mean systolic and diastolic blood pressure values were 109 ± 10 and 70 ± 8 mmHg, respectively. Baseline mean urea (23.7 ± 5.6 mg/dL), creatinine (0.35 ± 0.07 mg/dL), alanine transaminase (35.3 ± 10.6 U/L), and aspartate transaminase (46 ± 15.6 U/L) levels of the subjects were within normal limits. The mean pre-transfusion and post-transfusion hemoglobin level was 7.8 ± 0.9 g/dL and 11.8 ± 1.1 g/ dL, respectively. The mean serum ferritin level was 2017 ± 1573 ng/mL. All participants received iron chelation therapy; deferasirox in 26 patients, deferiprone in 2 patients, and combined deferasirox and deferiprone in 5 patients. Ten patients were splenectomized. In the study group, 30 of the patients had vitamin D deficiency and 3 had insufficiency. All patients had normal calcium, phosphorus, alkaline phosphatase, and parathyroid hormone levels. None of our patients received multivitamin and/or calcium channel blocker therapy.

Twelve patients had cardiac iron overload with T2* MR (Magnetic resonance) < 20 msn. In echocardiographic evaluation, the mean LVEF of patients without cardiac iron overload was 66.5 ± 2.9% while LVEF of patients with cardiac iron overload was 65.3 ± 3.7% ($P > 0.05$).

Speckle-tracking analysis showed no statistically significant difference between patients with and without cardiac iron overload (absolute values of LVGLS, LVGCS, and RVGLS) (Table 1).

Vitamin D treatment was given to patients who had vitamin D deficiency or insufficiency. Three months later, cardiological evaluations of the patients were performed when the patient's vitamin D level was normal. Patients' cardiological evaluations were compared before and after vitamin D replacement. A statistically significant difference in left ventricular functions before and after vitamin D replacement in conventional echocardiography was not detected (Table 2). In STE, the patients' LVGLS and LVGCS were 19 ± 2.7% and 20 ± 2.8% before vitamin D replacement, and LVGLS and LVGCS after vitamin D replacement were 24 ± 2.7% and 25 ± 3.8%, respectively $P = 0.001$, $P = 0.001$. A significant improvement in the global longitudinal strain of the left ventricular after vitamin D replacement was detected. There were significant improvements in the LV isovolumetric contraction time and isovolumetric relaxation time after the correction of vitamin D deficiency. Table 2 shows significant improvement of the abnormal strain in the vitamin D deficiency group after receiving vitamin D replasman therapy.

However, RVGLS did not show a significant improvement before and after vitamin D replacement.

Discussion

To the best of our knowledge, this is the first study that assessed the effect of vitamin D replacement on both LV and RV function in children with thalassemia major using STE. Speckle-tracking echocardiography is a feasible method for evaluating subclinical myocardial dysfunction and has been recently started to be used widely for children. Global longitudinal strain is a sensitive tool in the assessment of left ventricular function and changes in the LVGLS often occur before overt changes in the LVEF.[11]

Table 1. Echocardiographic and Speckle-Tracking Echocardiographic Evaluation of Patients With and Without Iron Overload in T2* MR

	T2* MR > 20 msn (n=21)	T2* MR < 20 msn (n=12)	*P*
LVEF (%)	66.5 ± 2.9	65.3 ± 3.7	0.75
LVGLS (%)	19.6 ± 2.8	20.4 ± 3.9	0.15
LVGCS (%)	20.9 ± 2.7	20.8 ± 2.3	0.92
RVGLS (%)	19.4 ± 3.4	19.9 ± 3.7	0.58

LVEF, left ventricular ejection fraction; LVGCS, left ventricular regional global circumferential strain; LVGLS, left ventricular global longitudinal strain; RVGLS, right ventricular global longitudinal strain.

Table 2. Left Ventricular Function and Speckle-Tracking Echocardiography Measurements of Patients Before and After Vitamin D Replacement

	Before Vitamin D Replacement	After Vitamin D Replacement	*P*
LVEF (%)	64 ± 4.7	65.1 ± 5.2	0.65
LVFS (%)	34.2 ± 3.8	35 ± 3.7	0.58
LVGLS (%)	19 ± 2.7	24 ± 2.7	0.042
LVGLSR (s^{-1})	0.8 ± 0.2	0.91 ± 0.19	
LVGCS (%)	20 ± 2.8	25 ± 3.8	0.034
LVGCSR (s^{-1})	0.78 ± 0.2	0.88 ± 0.21	
RVGLS (%)	19.4 ± 3.5	22.7 ± 4.1	>0.05
RVGLSR (s^{-1})	0.71 ± 0.21	0.8 ± 0.2	
LV E/A (ms)	1.2 ± 0.7	1.6 ± 0.9	0.01
LV IVCT (ms)	61.4 ± 8.7	59.7 ± 7.8	0.02
LV IVRT (ms)	59.7 ± 7.1	54.6 ± 9.1	0.04
LV ET (ms)	272.5 ± 18.8	260.1 ± 26	0.04

ET, ejection time; IVCT, isovolumetric contraction time; IVRT, isovolumetric relaxation time; LVEF, left ventricular ejection fraction; LVGCS, left ventricular regional global circumferential strain; LVGLS, left ventricular global longitudinal strain; LVFS, left ventricular fractional shortening; RVGLS, right ventricular global longitudinal strain; LVGLSR, left ventricular global longitudinal systolic strain rate.

Several factors are involved in the pathogenesis of the so-called "thalassaemic cardiomyopathy." In the era of systematic transfusion therapy, myocardial iron overload is traditionally thought to be the main cause of thalassemia cardiomyopathy.[12] Cardiac function in patients with thalassemia is relatively complex. Patients usually have mild chronic anemia despite regular transfusion, which results in hyperdynamic circulation characterized by increased cardiac output.[13] Cardiac iron overload is part of the complexity that induces oxidative damage by generating reactive oxygen species and results in heart failure.[14] Another cause of cardiac dysfunction is nutritional deficiencies such as vitamin D, selenium, zinc, copper, and thiamine.[15] In thalassemia major patients, defective synthesis of 25-OH vitamin D has been described and becomes an important cause of morbidity.[16] The deficiency of vitamin D reduces contractility of the heart muscle and increases the production of PTH, which in turn increases heart rate and cardiac hypertrophy and also increases cardiac iron uptake, leading to iron-induced cardiomyopathy.[17] Both PTH and 25-OH vitamin D appear to stimulate transmembrane calcium movement via L-type voltage-dependent calcium channels, which are important in transporting non-transferrin-bound iron into the myocardium.[18] Because of this, vitamin D levels should be assessed in thalassemia patients and replacement should be started if these levels are low.[19]

In patients with transfusion-dependent thalassemia, features of diastolic dysfunction appear to be present though the ejection fraction and the myocardial iron load are normal.[20] Balci and Gurses[21] demonstrated that in patients with thalassemia major, diastolic functions in tissue Doppler imaging were significantly impaired compared with the thalassemia trait patients and healthy children.[21] However, studies evaluating myocardial function in thalassemia patients with STE are limited in the literature.[22] Parsaee et al reported a significant reduction in global longitudinal strain and basal segments longitudinal strain compared to the normal subjects and concluded that STE helps to detect the early stages of left ventricular dysfunction in thalassemic patients.[8] Abtahi et al[23] reported that global longitudinal strain had a statistically significant correlation with T2* MR values and when taking a threshold of 19.5 as the cut-off value, it could detect iron deposition with a sensitivity of 82.14% and a specificity of 86.36%. Also, the assessment of global longitudinal strain can be used as a useful and less expensive tool for screening myocardial iron overload.[23]

In our study, a significant positive correlation between vitamin D level and left ventricular diastolic functions was detected in transfusion-dependent thalassemia patients with vitamin D deficiency. The relationship between vitamin D deficiency and cardiac function in patients with thalassemia has also been shown. Wood et al have reported that patients with low vitamin D levels have higher cardiac iron overload and significantly lower LVEF.[19] Ambarwati et al[24] reported that N-terminal pro-brain natriuretic peptide levels, which can be used to diagnose preclinical cardiac dysfunction, were higher in thalassemia major children with vitamin D deficiency than those with normal vitamin D levels. They also stated that thalassemic patients with cardiac dysfunction in conventional echocardiography have significantly lower vitamin D levels.

Some of the previous studies compared left ventricular global longitudinal strain and cardiac T2* MR in terms of cardiac functions in patients with thalassemia. These studies showed a significant correlation between LVGLS and cardiac T2*MR in patients with β-TM and patients with cardiac iron overload had a lower GLS than those without.[23,25] But, we did not find a statistically significant difference in the absolute value of LVGLS, LVGCS, and RVGLS between patients with and without cardiac iron overload. The reason for the lack of a statistical difference may be due to the small number of patients.

In patients with β-TM, diastolic functions deteriorate earlier than systolic functions in iron overload. Nadar et al[20] showed the presence of significant diastolic dysfunction with STE even in the presence of normal systolic function.[20] In our study, we also demonstrated that patients' diastolic functions had improved after vitamin D replacement therapy. Contrarily, in a recent study, it was found that vitamin D deficiency was associated with systolic dysfunction in patients with thalassemia.[26]

Study Limitations

Our study has some limitations such as the small number of patients. One of the limitations is that we did not compare patients with thalassemia major with normal vitamin D levels. Compliance with chelation therapy was self-reported but during every monthly visit, the importance of compliance with the chelating therapy was emphasized to the patients and their families. The effects of other nutritional deficiencies on cardiac dysfunction were not assessed in this study. Indeed, repeated vitamin D levels and LVGLS measurements across time could be useful to support our hypothesis.

Conclusion

Vitamin D deficiency is a severe complication of transfusion-dependent thalassemia in children. This study demonstrated that lower vitamin D levels were significantly associated with impaired myocardial deformation parameters, sufficient vitamin D substitution can be beneficial to improve the cardiac functions in patients with thalassemia major, and the STE can be used as a cheap and readily available non-invasive technique for the follow-up of patient's cardiac functions. Therefore, patients need regular monitoring of serum vitamin D levels to diagnose vitamin D deficiency early to reduce its complications. Further studies with more subjects and a longer follow-up period will be needed for a more precise assessment.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Pediatrics Hematology Oncology Training and Research Hospital of Ankara Health Sciences University (Approval No: May, 2019/173).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.K.Y, E.A., N.Y.; Design – A.K.Y, E.A., N.Y.; Supervision – A.K.Y.; Funding – A.K.Y, E.A.; Materials – A.K.Y, E.A.; Data Collection and/or Processing –A.K.Y, E.A., D.K., M.I., Ö.A.B., Z.G.; Analysis and/or Interpretation – A.K.Y., E.A.; Literature Review – A.K.Y., E.A., İ.İ.Ç., N.Y.Ö., N.Y.; Writing – A.K.Y., E.A., N.Y.; Critical Review – A.K.Y., E.A., N.Y.Ö., N.Y.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: The authors declare that this study had received no financial support.

References

1. Origa R. Beta-thalassemia. *Genet Med*. 2017;19(6):609-619. [CrossRef]
2. Marcon A, Motta I, Taher AT, Cappellini MD. Clinical complications and their management. *Hematol Oncol Clin North Am*. 2018;32(2):223-236. [CrossRef]
3. Wu HP, Lin CL, Chang YC, et al. Survival and complication rates in patients with thalassemia major in Taiwan. *Pediatr Blood Cancer*. 2017;64(1):135-138. [CrossRef]
4. Wasson LT, Shimbo D, Rubin MR, Shaffer JA, Schwartz JE, Davidson KW. Is vitamin D deficiency a risk factor for ischemic heart disease in patients with established cardiovascular disease? 10-year follow-up of the Nova Scotia Health Survey. *Int J Cardiol*. 2011;148(3):387-389. [CrossRef]
5. Brown SJ, Ruppe MD, Tabatabai LS. The parathyroid gland and heart disease. *Methodist Debakey CardioVasc J*. 2017;13(2):49-54. [CrossRef]
6. Bansal N, Zelnick L, Robinson-Cohen C, et al. Serum parathyroid hormone and 25-hydroxyvitamin D concentrations and risk of incident heart failure: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2014;3(6):e001278. [CrossRef]
7. Somjen D, Weisman Y, Kohen F, et al. 25-Hydroxyvitamin D3-1alpha-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. *Circulation*. 2005;111(13):1666-1671. [CrossRef]
8. Parsaee M, Saedi S, Joghataei P, Azarkeivan A, Alizadeh Sani Z. Value of speckle tracking echocardiography for detection of clinically silent left ventricular dysfunction in patients with beta-thalassemia. *Hematology*. 2017;22(9):554-558. [CrossRef]
9. Geyer H, Caracciolo G, Abe H, et al. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. *J Am Soc Echocardiogr*. 2010;23(4):351-369; quiz 453-455. [CrossRef]
10. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233-270. [CrossRef]
11. Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? *Eur Heart J*. 2016;37(15):1196-1207. [CrossRef]
12. Rund D, Rachmilewitz E. Beta-thalassemia. *N Engl J Med*. 2005;353(11):1135-1146. [CrossRef]
13. Walker JM. Thalassaemia major and the heart: a toxic cardiomyopathy tamed? *Heart*. 2013;99(12):827-834. [CrossRef]
14. Berdoukas V, Coates TD, Cabantchik ZI. Iron and oxidative stress in cardiomyopathy in thalassemia. *Free Radic Biol Med*. 2015;88(A):3-9. [CrossRef]
15. Wood JC. Cardiac complications in thalassemia major. *Hemoglobin*. 2009;33(Suppl 1)(suppl 1):S81-S86. [CrossRef]
16. Aloia JF, Ostuni JA, Yeh JK, Zaino EC. Combined vitamin D parathyroid defect in thalassemia major. *Arch Intern Med*. 1982;142(4):831-832. [CrossRef]
17. Oudit GY, Sun H, Trivieri MG, et al. L-type Ca2+ channels provide a major pathway for iron entry into cardiomyocytes in iron-overload cardiomyopathy. *Nat Med*. 2003;9(9):1187-1194. [CrossRef]
18. Holick MF. The influence of vitamin D on bone health across the life cycle. *J Nutr*. 2005;135(11):2726S-2727S. [CrossRef]
19. Wood JC, Claster S, Carson S, et al. Vitamin D deficiency, cardiac iron and cardiac function in thalassaemia major. *Br J Haematol*. 2008;141(6):891-894. [CrossRef]
20. Nadar SK, Daar S, Abdelmottaleb WA, et al. Abnormal diastolic function and Global longitudinal strain in patients with thalassemia major on long term chelation therapy. *Int J Cardiovasc Imaging*. 2021;37(2):643-649. [CrossRef]
21. Balci YI, Gurses D. Detection of early cardiac dysfunction in patients with beta-thalassemia major and thalassemia trait by tissue doppler echocardiography. *Pediatr Hematol Oncol*. 2011;28(6):486-496. [CrossRef]
22. Cheung YF, Liang XC, Chan GC, Wong SJ, Ha SY. Myocardial deformation in patients with Beta-thalassemia major: a speckle tracking echocardiographic study. *Echocardiography*. 2010;27(3):253-259. [CrossRef]
23. Abtahi F, Abdi A, Jamshidi S, Karimi M, Babaei-Beigi MA, Attar A. Global longitudinal strain as an Indicator of cardiac Iron overload in thalassemia patients. *Cardiovasc Ultrasound*. 2019;17(1):24. [CrossRef]
24. Ambarwati L, Rahayuningsih SE, Setiabudiawan B. Association between vitamin D levels and left ventricular function and NT-proBNP levels among thalassemia major children with iron overload. *Ann Pediatr Cardiol*. 2016;9(2):126-131. [CrossRef]
25. Parsaee M, Akiash N, Azarkeivan A, et al. The correlation between cardiac magnetic resonance T2* and left ventricular global longitudinal strain in people with beta-thalassemia. *Echocardiography*. 2018;35(4):438-444. [CrossRef]
26. Pishgahi M, Niroomand M, Bozorgmehr R, et al. Association between serum vitamin D level and echocardiographic abnormalities in patients with thalassemia major. *Cardiovasc Hematol Disord Drug Targets*. 2020;20(3):214-220. [CrossRef]

The Effects of Vitamin D on Myocardial Function Demonstrated by Speckle-Tracking Echocardiography in Children with Beta Thalassemia

33 Thalassemic pts
w/ Vitamin D deficiency

	Before Vitamin D Replacement		After Vitamin D Replacement	
LVEF (%)	64 ± 4.7	vs.	65.1 ± 5.2	P <0.05
RVGLS (%)	19.4 ± 3.5	vs.	22.7 ± 4.1	P <0.05
LVGLS (%)	19 ± 2.7	vs.	24 ± 2.7	P =0.04
LVGCS (%)	20 ± 2.8	vs.	25 ± 3.8	P =0.03

Vitamin D deficiency is frequently observed and causes decreased contractility in thalassemic patients. Patients' cardiac functions may improve after vitamin D replacement therapy.

@PAY 2023