*Cardiology in the Young*

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# Can biomarkers predict myocardial iron overload in children with thalassemia major?

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## Original Article

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## Abstract

*Aim:* Beta-thalassemia major requires regular blood transfusions throughout life, which in turn leads to iron accumulation in the body. While cardiac T2* MRI is the gold standard in determining cardiac iron accumulation, it is not always feasible, which has led to the search for new biomarkers. Herein, the value of growth differentiation factor-15, galectin-3, and N-terminal pro-B-type natriuretic peptide in predicting cardiac iron accumulation is investigated in asymptomatic children with beta-thalassemia major. *Materials and method:* Forty-one patients aged 11–21 years and 41 age-, gender-, body mass index-matched healthy controls were included. Serum growth differentiation factor-15, galectin-3, and N-terminal pro-B-type natriuretic peptide levels were compared between the patients and controls. Additionally, the relations of these biomarkers with cardiac and liver T2 * MRI were investigated in the patients. *Results:* In the patients, growth differentiation factor-15, galectin-3, and N-terminal pro-B-type natriuretic peptide levels were higher than healthy controls ($p < 0.001$, $p = 0.025$, $p < 0.001$, respectively). There were no significant correlations of growth differentiation factor-15 and N-terminal pro-B-type natriuretic peptide levels with both cardiac and liver T2 * MRI measurements. While there was no significant correlation of serum galectin-3 with cardiac T2 * MRI measurements, a negative correlation was found with liver T2 * MRI measurements ($p = 0.040$, rho = –0.325). *Conclusion:* All three biomarkers investigated in this study failed to predict myocardial iron accumulation in asymptomatic children with beta-thalassemia major. However, a weak relation between serum galectin-3 level and hepatic iron accumulation was demonstrated.

## Introduction

Beta-thalassemia major is a disorder caused by a defect in the beta-chain of hemoglobin. It requires regular blood transfusions throughout life, which in turn leads to iron accumulation in the body. Cardiac complications due to iron accumulation are the most common cause of death in these patients, and iron-chelation therapy helps to prevent these complications. Initiation of chelation therapy or dose adjustment is planned according to cardiac relaxation time T2* MRI and serum ferritin level.[1] While cardiac T2 * MRI is the gold standard in determining cardiac iron accumulation, it is not always feasible, may require sedation and the scan time is long, which has led to the search for a new biomarker.[2]

Growth differentiation factor-15 is a protein involved in tissue homeostasis, differentiation, remodeling, and repair. It is elevated in acute injury, tissue hypoxia, and inflammation.[3,4] Galectin-3 is a protein that has been implicated in the pathogenesis of many inflammatory, autoimmune conditions, and cardiovascular remodeling.[4–6] N-terminal pro-B-type natriuretic peptide is secreted in response to cardiac stress and volume overload.[7] It helps to detect asymptomatic left ventricular dysfunction in the early diagnosis of cardiac disease.

In this study, the values of serum growth differentiation factor-15, galectin-3, and N-terminal pro-B-type natriuretic peptide in predicting myocardial iron accumulation based on cardiac T2 * MRI measurements are investigated in asymptomatic children with beta-thalassemia major. In addition, it was aimed to compare the levels of these markers in children with beta-thalassemia major with those in healthy children.

## Materials and method

### Study design and selection of participants

This is a cross-sectional study conducted between January 2020 and February 2020. The patients aged 11–21 years who were diagnosed with beta-thalassemia major using hemoglobin electrophoresis and/or genetic mutation analysis from three different tertiary centers and age-, gender-, and body mass index-matched healthy controls were included in the study. Patients with congenital/acquired heart disease, chronic kidney disease, hepatic failure, autoimmune disease, and infectious disease were excluded from the study. In addition, patients and controls were evaluated with two-dimensional echocardiography along with an electrocardiogram (ECG) by an experienced pediatric cardiologist. Children with cardiac dysfunction were not included in either group.

All procedures contributing to this work comply with the ethical standards of the national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was approved by the Clinical Research Ethical Committee of Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty (A-13 on November 15, 2019). Written informed consent for participation in the study was obtained from all participants and their parents.

### Data collection and clinical evaluation

Patients' age, gender, age at diagnosis and onset of chelation, the total number of erythrocyte transfusions received and mean serum ferritin level in the last year were obtained from the medical records.

Anthropometric measurements of the patients and controls were made, and body mass index and body surface area were calculated. Standard deviation scores of height, weight, and body mass index were calculated according to the normal values of Turkish children.[8,9] Blood pressure was measured in all participants.

### Laboratory investigation and imaging

Complete blood count, serum urea, creatinine, transaminases, C-reactive protein, and thyroid function tests were measured in all participants. Patients' viral serology for hepatitis B, C, and human immunodeficiency virus was checked from their medical records. Three centiliters of serum samples were obtained from the patients one day before erythrocyte transfusion and also from the healthy controls. The collected samples were centrifuged and stored at –80°C. In these samples, three biomarkers were analysed: growth differentiation factor-15 and galectin-3 with enzyme-linked immunoassay (ELISA) method (Thermo Scientific™, Massachusetts, USA) and N-terminal pro-B-type natriuretic peptide with chemiluminescence method (Roche Diagnostics™, Cobas E 411, Mannheim, Germany).

Relaxation time T2 * MRI was performed using a 1.5 Tesla MRI scanner (Ingenia, Philips Medical Systems; Best, Netherlands) with a 32-channeled phased-array torso coil. For cardiac imaging, each image was performed with a cardiac-gated, single-breath-hold gradient echo sequence of a single mid-ventricular short-axis slice with 15 different echo times. First TE: 1.27 ms, delta TE: 1.4 ms, TR: 22 ms, FA: 20°, matrix size: 224x226, FOV: 450 mm, ST: 10 mm, gap: 0, scan time: 00:24.

For the liver, the mDIXON-Quant sequence was acquired with a single-breath-hold transaxial slice of the liver and the imaging protocol was time of repetition (TR): 5.3 ms, number of echoes: 6, first echo time (TE): 0.92 ms, delta TE: 0.7 ms, flip angle (FA): 5°, matrix size: 132 × 118 mm, the field of view (FOV): 400 mm, slice thickness: 6 mm, gap: –3, scan time (min: sec): 00:12.

Magnetic resonance imaging of all participants was evaluated by the same experienced pediatric radiologist. Data analyses were performed at the workstation using dedicated software (Extended MR workspace version 2.5.3.1, Philips Medical Systems; Best, Netherlands) with regions of the interventricular septum for the heart and the largest regions of interest excluding vascular structures for the liver.

Cardiac T2 * MRI measures > 20 ms were determined as normal, which indicates an insignificant degree of myocardial iron deposition, 10–20 ms as moderate, and < 10 ms as severe iron accumulation. For liver T2 * MRI, the measurements > 6.3 ms were determined as normal, 2.7–6.3 ms as mild, 1.4–2.7 ms as moderate, and < 1.4 ms as severe accumulation.[10]

### Statistics

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software for Windows, version 22 (Chicago, Illinois). The variables were investigated using visual (histograms) and analytical methods (Shapiro–Wilk's test) to determine if the data were normally distributed. Data were presented as mean and standard deviation for normally distributed variables and median (minimum–maximum) for non-normally distributed variables. Student's *t*-test or Mann–Whitney *U*-test was used according to the distribution status to compare two independent groups. To compare the paired groups, paired sample *t*-test or Wilcoxon test was used. Spearman correlation analysis was used for non-normally distributed continuous variables. The statistical significance was accepted as a p-value of < 0.05. The post-hoc power of the study was calculated as 87% at an alpha level of 0.05 using Gpower 3.1.9.2.

## Results

The study included 41 patients with beta-thalassemia major and the same number of healthy controls. There was no statistical difference between the patients and controls in terms of mean age, standard deviation scores of body mass index, and gender distribution (17.2 ± 3.1 vs. 17.1 ± 3.2 years, p = 0.347; –0.87 ± 1.26 vs. –0.75 ± 1.19, p = 0.606, respectively, and male: female = 28:13 in both groups).

All participants had normal thyroid function tests, serum urea, creatinine, transaminases, and CRP and negative viral serology for hepatitis B, C, and human immunodeficiency virus. Also, both patients and controls had normal ECG, normal left ventricular systolic functions on echocardiography, and normal blood pressure according to age, gender, and height. The clinical, laboratory, and imaging data of the patients are shown in Table 1.

In cardiac T2 * MRI, 31 patients had normal measurements, 6 had moderate, and 4 had severe iron accumulation. Liver T2 * MRI was performed in 38 patients, and 15 had normal measurements, 10 had mild, 5 had moderate, and 8 had severe iron accumulation. Cardiac and liver T2 * MRI measurements were correlated with each other (p < 0.001, rho = 0.654) (Fig 1).

Growth differentiation factor-15, galectin-3, and N-terminal pro-B-type natriuretic peptide levels were found to be significantly higher in the patients compared to the controls. Table 2 shows the serum biomarker levels of the patients and controls.

When the patient group was divided into two subgroups according to cardiac T2 * MRI measurements (normal and those

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**Table 1.** Clinical and laboratory data of the patients

| | |
|---|---|
| Age at diagnosis (months) | 10.5 (0–72) |
| Age at chelation onset (months) | 36.5 (12–156) |
| Transfusion amount (unit/year) | 31.24 ± 7.85 |
| Mean ferritin in the preceding year (ng/mL) | 1084.36 (563.29–4958.09) |
| Hemoglobin level (g/dL) | 9.00 ± 0.55 |

Data are presented as mean ± standart deviation or median (minimum–maximum) depending on the distribution.

with iron accumulation), there was no significant difference in terms of growth differentiation factor-15, galectin-3, and N-terminal pro-B-type natriuretic peptide levels ($p = 0.379$, $p = 0.202$, $p = 0.225$, respectively). Only the mean annual ferritin level was significantly higher in patients with iron accumulation ($p = 0.002$). Similarly, when two subgroups were created according to liver measurements, a significant difference was found in terms of galectin-3 and mean annual ferritin levels ($p = 0.032$ and $p = 0.003$, respectively). These biomarkers were higher in the subgroup with iron accumulation. There was no significant difference between the two subgroups in terms of serum growth differentiation factor-15 and N-terminal pro-B-type natriuretic peptide levels ($p = 0.068$, $p = 0.276$, respectively).

There was no statistically significant correlation between serum growth differentiation factor-15 and N-terminal pro-B-type natriuretic peptide levels with both cardiac and liver T2 * MRI measurements (for growth differentiation factor-15 $p = 0.863$, $p = 0.066$, respectively) (for N-terminal pro-B-type natriuretic peptide $p = 0.609$, $p = 0.790$, respectively). While there was no statistically significant correlation of serum galectin-3 with cardiac T2 * MRI measurements, a weak negative correlation was found with liver T2 * MRI measurements ($p = 0.040$, rho = –0.325). A statistically significant negative correlation of mean annual serum ferritin level was found between both cardiac T2 * MRI ($p < 0.001$, rho = –0.563) and liver T2 * MRI measurements ($p < 0.001$, rho = 0.589) Table 3.

## Discussion

The main finding of this study is the inability of the serum growth differentiation factor-15, galectin-3, and N-terminal pro-B-type natriuretic peptide levels to detect cardiac iron accumulation in asymptomatic children with beta-thalassemia major. There was a weak relationship between serum galectin-3 levels and iron accumulation in the liver. Ferritin is a good marker to evaluate cardiac and liver iron accumulation. Serum growth differentiation factor-15, galectin-3, and N-terminal pro-B-type natriuretic peptide levels were found to be higher in children with beta-thalassemia major compared to healthy children, while similar levels were found in patients with or without cardiac iron accumulation.

Growth differentiation factor-15 is a cytokine that increases in cardiomyocytes in response to stress, inflammation, and tissue damage. In cases of stress, such as erythroblast apoptosis in the bone marrow, it reaches high levels in relation to ineffective erythropoiesis.[11] In this study, the growth differentiation factor-15 value in children with beta-thalassemia major was found to be approximately 12 times higher than in healthy children. Similarly, high levels of growth differentiation factor-15 have been shown in previous studies conducted in patients with both beta-thalassemia major and thalassemia intermedia.[12,13] Pasricha et al.[14] investigated the association of growth differentiation factor-15 with ineffective erythropoiesis and bone marrow stress by measuring growth differentiation factor-15 levels both before and after transfusion. Growth differentiation factor-15 levels were shown to be significantly higher before the transfusion compared to 4–8 days after the transfusion. This finding suggested that growth differentiation factor-15 could reflect the effectiveness of the frequency and amount of erythrocyte transfusion. Our study is the first to investigate the relationship between growth differentiation factor-15 level and cardiac T2 * MRI in patients with beta-thalassemia major. Growth differentiation factor-15 was not associated with the level of cardiac and liver iron accumulation, and their elevated levels in our patients compared with healthy children were attributed to ineffective erythropoiesis or factors other than cardiac iron accumulation, such as anemia and hypoxia.

Galectin-3 is a product of activated macrophages that bind to cardiac fibroblasts. Its increased levels indirectly reflect increased myocardial collagen secretion, interstitial fibrosis, transforming growth factor-beta activation, and thus left ventricular dysfunction.[5,15] It also has a role in ventricular remodeling as well as the damage and inflammation seen in heart failure.[16] In this study, while serum galectin-3 levels did not show a significant correlation with cardiac iron accumulation, it was weakly correlated with hepatic iron accumulation. The relationship between serum galectin-3 levels and cardiac iron accumulation in beta-thalassemia major has been previously investigated in adults, and likewise, no correlation was found.[17] Galectin-3 levels were found to be higher in our children with beta-thalassemia major compared to healthy children, which may be attributed to inflammation and fibrosis due to factors other than cardiac iron accumulation, such as anemia and hypoxia. In our study, despite the presence of a correlation of serum galectin-3 levels with liver iron accumulation, a relation with cardiac iron accumulation could not be demonstrated. This may be because the patients with severe cardiac iron accumulation, unlike those with severe liver iron accumulation, were few in number.

N-terminal pro-B-type natriuretic peptide released from the ventricles due to cardiac stress and volume overload reduces the preload with its natriuretic effect.[7] In previous studies conducted with patients with beta-thalassemia major, N-terminal pro-B-type natriuretic peptide is a sensitive biomarker to detect systolic and diastolic dysfunction.[18–21] Elevated N-terminal pro-B-type natriuretic peptide levels have been shown in both adult and pediatric patients with beta-thalassemia major. In this study, no correlation could be found between serum N-terminal pro-B-type natriuretic peptide level and cardiac iron accumulation, which was supported by previous studies.[20,22] Several studies investigated whether plasma N-terminal pro-B-type natriuretic peptide levels are predictive of cardiac iron accumulation, based on cardiac T2* assessment by MRI. Kautsar et al.[22] studied 68 children with beta-thalassemia major with a median age of 14 years with no signs of heart failure and showed no significant correlation of N-terminal pro-B-type natriuretic peptide and cardiac T2 * MRI as in our study. Accordingly, N-terminal pro-B-type natriuretic peptide levels were not different between the patients with and without cardiac iron accumulation. Likewise, Mehrzad et al.[21] evaluated serum N-terminal pro-B-type natriuretic peptide levels in 50 adults with beta-thalassemia major aged 18–46 years with preserved left

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**Table 2.** Biomarker levels and T2* magnetic resonance imaging measurements

| | Patients | Controls | *p* |
|---|---|---|---|
| GDF-15 (pg/mL) | 10781.99 (1116.68 – 12438.12) | 754.38 (532.55 – 1038.64) | < **0.001** |
| Galectin-3 (ng/mL) | 14.7 (8.8 – 68.1) | 12.65 (7.94 – 24.45) | **0.025** |
| NT-proBNP (pg/mL) | 60.98 (28.35 – 235.7) | 32.73 (14.11 – 99.1) | < **0.001** |
| Cardiac T2 * MRI (ms) | 28.76 ± 11.62 | – | |
| Liver T2 * MRI (ms) | 4.5 (0.9–18) | – | |

Data are presented as mean ± standart deviation or median (minimum–maximum) depending on the distribution.
GDF-15: growth differentiation factor-15, NT-proBNP: N-terminal pro-B-type natriuretic peptide.
Bold shows statistical significance.

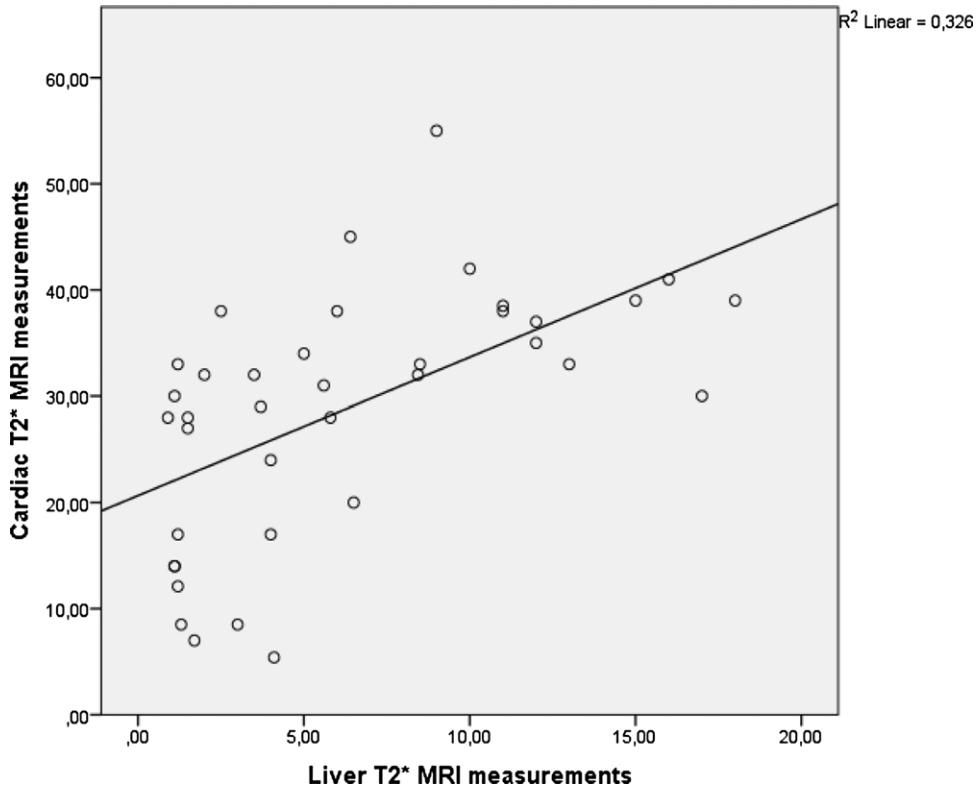


**Figure 1.** The correlation of cardiac and liver T2* MRI measurements.

ventricular systolic function and found no correlation with cardiac iron accumulation.[21] On the contrary, Goudarzipour et al.[23] reported a strong correlation between N-terminal pro-B-type natriuretic peptide and cardiac T2 * MRI in 35 children with beta-thalassemia major at a mean age of 17 years. Of these, 26 (75%) had cardiac iron accumulation and 2 had heart failure. Our study includes a limited number of patients with cardiac iron accumulation, which may explain the absence of a significant correlation between N-terminal pro-B-type natriuretic peptide levels and cardiac iron accumulation even though the levels of N-terminal pro-B-type natriuretic peptide were higher in our patients compared with healthy children. High levels of N-terminal pro-B-type natriuretic peptide in beta-thalassemia major may be due to anemia rather than cardiac iron accumulation. Anemia is known to increase N-terminal pro-B-type natriuretic peptide levels. It causes tachycardia and increased cardiac output resulting in transmural wall stress. Also, fluid retention caused by the decrease in renal blood flow increases cardiac stress even more. Lastly, it has been suggested that changes in volume balance may have a direct effect on the levels of natriuretic peptides.[24]

In our study, a moderate negative correlation of mean annual serum ferritin level was found with both cardiac and liver T2 * MRI measurements, which is consistent with previous pediatric and adult studies.[25–27] In this regard, although a strong correlation could not be demonstrated, it may be inferred that serum ferritin is still the best indicator for monitoring iron accumulation and regulating chelation therapy in centers where T2 * MRI cannot be performed.

The strength of the study was that biomarker levels were compared with T2 * MRI, which is the gold standard method for detecting iron accumulation; however, the small number of patients with severe iron deposition limited this investigation.

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**Table 3.** The correlation of cardiac and liver T2 * MRI measurements with biomarkers (rho values)

| | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| 1. Cardiac T2 * MRI (n = 41) | 1.000 | | | | | |
| 2. Liver T2 * MRI (n = 38) | 0.659** | 1.000 | | | | |
| 3. NT-proBNP (pg/mL) | −0.082 | −0.045 | 1.000 | | | |
| 4. GDF-15 (pg/mL) | 0.028 | −0.301 | 0.065 | 1.000 | | |
| 5. Galectin-3 (ng/mL) | −0.089 | −0.325* | 0.061 | 0.497** | 1.000 | |
| 6. Mean annual ferritin (ng/mL) | 0.563** | −0.589** | 0.245 | −0.063 | −0.012 | 1.000 |

*< 0.05, **< 0.01.
Spearman's rank correlation (rho) between the study variables.
GDF-15: growth differentiation factor-15, NT-proBNP: N-terminal B-type natriuretic peptide.

## Conclusion

Measurements of serum growth differentiation factor-15, galectin-3, and N-terminal pro-B-type natriuretic peptide levels are not sufficient for early detection of cardiac iron overload in asymptomatic children with beta-thalassemia major. Galectin-3 level, which is a precursor of early fibrosis, has been shown to be associated with iron accumulation in the liver. Since serum growth differentiation factor-15, galectin-3, and N-terminal pro-B-type natriuretic peptide levels were found to be higher in children with beta-thalassemia major compared to healthy children, these biomarkers may be useful to show cardiac involvement due to the factors other than cardiac iron loads, such as anemia and hypoxia.

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**Conflict of interest.** None.

**Ethical standards.** The authors assert that all procedures contributing to this work comply with the ethical standards of the national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 and has been approved by Cerrahpaşa Medical Faculty Ethic Committee (A-13, 15.11.2019). A written informed consent was taken from all participants and their parents.

## References

1. Needs T, Gonzalez-Mosquera LF, Lynch DT. Beta Thalassemia. StatPearls [Internet]. StatPearls Publishing, Treasure Island, 2022.
2. Shehata SM, Amin MI, Zidan ESH. MRI evaluation of hepatic and cardiac iron burden in pediatric thalassemia major patients: spectrum of findings by T2*. Egypt J Radiol Nucl Med 2019; 50: 1–9.
3. Xu J, Kimball TR, Lorenz JN, et al. GDF15/MIC-1 functions as a protective and antihypertrophic factor released from the myocardium in association with SMAD protein activation. Circ Res 2006; 98: 342–350.
4. Gudowska M, Gruszewska E, Cylwik B, et al. Galectin-3 concentration in liver diseases. Ann Clin Lab Sci 2015; 45: 669–673.
5. Bošnjak I, Selthofer-Relatic K, Včev A. Prognostic value of galectin-3 in patients with heart failure. Dis Markers 2015; 2015: 690205.
6. Sharma UC, Pokharel S, Van Brakel TJ, et al. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. Circulation 2004; 110: 3121–3128.
7. Daniels LB, Maisel AS. Natriuretic peptides. J Am Coll Cardiol 2007; 50: 2357–2368.
8. Neyzi O, Bundak R, Gökçay G, et al. Reference values for weight, height, head circumference, and body mass index in Turkish children. JCRPE J Clin Res Pediatr Endocrinol 2015; 7: 280–293.
9. Demir K, Özen S, Konakçı E, Aydın M, Darendeliler F. A comprehensive online calculator for pediatric endocrinologists: ÇEDD Çözüm/TPEDS Metrics. J Clin Res Pediatr Endocrinol 2017; 9: 182–184.
10. Kirk P, He T, Anderson LJ, et al. International reproducibility of single breathhold T2* MR for cardiac and liver iron assessment among five thalassemia centers. J Magn Reson Imaging 2010; 32: 315–319.
11. Larissi K, Politou M, Margeli A, et al. The growth differentiation factor-15 (GDF-15) levels are increased in patients with compound heterozygous sickle cell and beta-thalassemia (HbS/β thal), correlate with markers of hemolysis, iron burden, coagulation, endothelial dysfunction and pulmonary. Blood Cells, Mol Dis 2019; 77: 137–141.
12. Athiyarath R, Shaji RV, Ahmed R, et al. High expression of p53 and growth differentiation factor-15 in beta-thalassemia. Blood 2012; 17: 184–190.
13. Tanno T, Bhanu NV, Oneal PA, et al. High levels of GDF 15 in thalassemia suppress expression of the iron regulatory protein hepcidin. Nat Med 2007; 13: 1096–1101.
14. Pasricha SR, Frazer DM, Bowden DK, Anderson GJ. Transfusion suppresses erythropoiesis and increases hepcidin in adult patients with β-thalassemia major: a longitudinal study. Blood 2013; 122: 124–133.
15. Kotby AA, Youssef OI, Elmaraghy MO, El Sharkawy OS. Galectin-3 in children with chronic heart failure with normal and reduced ejection fraction: relationship to disease severity. Pediatr Cardiol 2017; 38: 95–102.
16. Ansari U, Behnes M, Hoffmann J, et al. Galectin-3 reflects the echocardiographic grades of left ventricular diastolic dysfunction. Ann Lab Med 2018; 38: 306–315.
17. Ricchi P, Meloni A, Di Matola T, et al. Galectin-3 and myocardial fibrosis by cardiac magnetic resonance in thalassaemia major. Blood 2016; 128: 4832.
18. Kremastinos DT, Hamodraka E, Parissis J, Tsiapras D, Dima K, Maisel A. Predictive value of B-type natriuretic peptides in detecting latent left ventricular diastolic dysfunction in β-thalassemia major. Am Heart J 2010; 159: 68–74.
19. Delaporta P, Kattamis A, Apostolakou F, et al. Correlation of NT-proBNP levels and cardiac iron concentration in patients with transfusion-dependent thalassemia major. Blood Cells, Mol Dis 2013; 50: 20–24.
20. Mehrzad V, Khajouei AS, Fahami E. Correlation of N-terminal pro-B-type natriuretic peptide levels and cardiac magnetic resonance imaging T2* in patients with β-thalassaemia major. Blood Transfus 2016; 14: 516–520.
21. Özyörük D, Öner T, Oymak Y, Çelik HT. Comparison of Doppler echocardiographic and tissue Doppler velocity data in beta-thalassaemia major with high and normal NT-proBNP levels of children in the south-east region of Turkey. Transl Pediatr 2014; 3: 287–292.
22. Kautsar A, Advani N, Andriastuti M. N-Terminal-pro-b-Type natriuretic peptide levels and cardiac hemosiderosis in adolescent β-Thalassemia major patients. Ann Pediatr Cardiol 2019; 12: 32–37.

https://doi.org/10.1017/S1047951122004206 Published online by Cambridge University Press

23. Goudarzipour K, Alizadeh P, Tavassol HH, Kazemi R, Eshghi P, Mojtahedzadeh S. A comparison between MRIT2 and NT-ProBNP in early detection of heart diseases in thalassemia major patients: a cross-sectional study. Indian J Hematol Blood Transfus 2017; 33: 541–544.
24. Matsumoto M, Tsujino T, Naito Y, et al. Anemia as a factor that elevates plasma brain natriuretic peptide concentration in apparently healthy subjects. Int Heart J 2008; 49: 577–586.
25. Chirico V, Rigoli L, Lacquaniti A, et al. Endocrinopathies, metabolic disorders, and iron overload in major and intermedia thalassemia: serum ferritin as diagnostic and predictive marker associated with liver and cardiac T2* MRI assessment. Eur J Haematol 2015; 94: 404–412.
26. Mandal S, Sodhi KS, Bansal D, et al. MRI for quantification of liver and cardiac iron in thalassemia major patients: Pilot Study in Indian Population. Indian J Pediatr 2017; 84: 276–282.
27. Eghbali A, Taherahmadi H, Shahbazi M, Bagheri B, Ebrahimi L. Association between serum ferritin level, cardiac and hepatic T2-star MRI in patients with major β-thalassemia. Iran J Pediatr Hematol Oncol 2014; 4: 17–21.

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