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RESEARCH ARTICLE

Relationship between serum ferritin and hemoglobin levels determined by cardiac and hepatic T2 MRI in beta-thalassemia intermedia and major patients

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BACKGROUND: Thalassemia major is one of the most common hereditary disorders, and it causes ineffective hematopoiesis in the body through disarrangement of the hemoglobin synthesis balance. Regular blood transfusions cause complications of iron overload in the body in these patients. Tissue iron status can be determined by measuring serum and liver biopsy ferritin levels and by T2* MRI. This study assessed the relationship between serum ferritin and hemoglobin by T2* MRI of the heart and liver.

METHOD: This cross-sectional descriptive study was carried out on patients with beta-thalassemia intermedia and major who visited the Center for Thalassemia and Hemoglobinopathies at Shafa Hospital, Ahwaz, between 2014 and 2015. All patients were receiving regular blood transfusions every 2−4 weeks. Pearson's correlation test was used to assess serum ferritin and T2* values from heart and liver MRI.

RESULTS: A total of 260 patients (mean age is 23-year-old) were enrolled in the study. The incidence of iron overload in the liver and heart was 83% and 39%, respectively. Serum ferritin levels showed a very strong inverse correlation with T2* values on heart ($r = -3.54$, $p < 0.0001$) and liver ($r = -3.03$, $p < 0.0001$) MRI. Additionally, a meaningful interaction was observed between the T2* values from liver and heart MRI ($r = 0.29$, $p < 0.0001$).

CONCLUSION: Serum ferritin is strongly and inversely correlated with T2* values of MRI of the liver and heart in patients with thalassemia. Therefore, T2* MRI can be used to assess tissue iron levels with very high accuracy.

Keywords Serum ferritin, thalassemia, T2* MRI, liver, heart, iron overload

Introduction

Thalassemia is a group of hereditary hematologic abnormalities that are inherited in an autosomal recessive manner; it causes imbalances in the synthesis of hemoglobin chains and eventually leads to ineffective hematopoiesis. Homozygosity for beta-thalassemia can cause both thalassemia major and intermedia. Regular blood transfusion is the most important maintenance therapy for these patients and is aimed at maintaining hemoglobin levels at 7−9 mg/dL. This treatment brings about normal growth to the age of 10 years. However, patients are exposed to increased risk of the complications of iron-overload after blood transfusion. Iron-overload in the body causes numerous complications for the patient, including hypogonadism (35%−55%), hypothyroidism (9%−11%), hypoparathyroidism (4%), diabetes (6%−10%), and hepatic fibrosis and heart failure (34%). Myocardial diseases are the most dangerous complication of iron overload, and seventy one percentof deaths in patients with thalassemia major are reportedly due to myocardial diseases. Thus, the iron status in patients receiving blood transfusions should constantly be monitored. Evaluation of serum iron levels by measuring ferritin is one of the simplest methods. It is noteworthy that this factor is not always reliable. Ferritin is an acute phase protein that increases under the influence of inflammatory diseases, such as liver disease and malignancies. Liver iron concentration in liver biopsy samples is strongly related to an

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accumulated iron in the body and is considered to be a gold standard for iron overload. However, this technique is associated with significant disadvantages, including its aggressiveness that results in damage, albeit minimal, to liver tissue, as well as the lack of distribution of iron in the liver, which may cause false negative results. However, magnetic resonance imaging (MRI) has been introduced as a non-invasive method for assessing levels of iron accumulated in the tissues that appears to offer similar results to the gold standard methods, and changing the therapeutic management of thalassemia patients. Therefore, evaluation of iron deposits in the body can be easily diagnosed before the onset of clinical symptoms.

T2-star magnetic resonance imaging (T2* MRI) allows evaluation of complexes with high molecular weight iron levels, such as ferritin and hemosiderin, which will, in turn, induce an increase in T2 relaxation. This method is now available worldwide and is widely used for assessing the amount of iron deposited in the heart and liver. We investigated the relationship between hemoglobin, as the main source of iron, and serum ferritin levels, based on T2* MRI analysis of the liver and heart.

Materials and methods

Subjects

This cross-sectional study was carried out on patients with beta-thalassemia intermedia and major, who visited the Center for Thalassemia and Hemoglobinopathies at Shafa Hospital, Ahwaz, between 2014 and 2015. Patients included all patients with thalassemia major and intermedia who typically received regular blood transfusions at 2−4 week intervals, in order to maintain hemoglobin levels between 7 and 9 g/dL (10 mL red blood cell [RBC] packed cells per kilogram of bodyweight). Hepatitis B and C patients were excluded from the study in order to avoid overload due to iron chelation by deferoxaminemesylate (30−40 mg/kg daily for 4−5 days per week), due to their effect in the amount of ferritin. This study was approved by the Ethics Committee of the Medical University of Ahwaz, and all patients gave improved consent.

Ferritin measurement

Ferritin measurement was conducted by electrochemiluminescence (Elecsys 2010 Chemistry Analyzer, Roche Diagnostics, Basel, Switzerland). Measurement of hemoglobin was conducted by cell counter system.

MRI protocol

MRI was performed at the Imaging Center of Ahwaz Golestan Hospital in Iran, using a 1.5 Tesla scanner (Achieva 1.5T A-series, Philips Medical Systems,USA) for all patients.

A standard RF body coil was used for all measurements. The Royal Brompton protocol was used to conduct MRIs. The scans were synchronized with cardiac cycles using a standard ECG port for the measurement of myocardial T2*. Then, a short axis of 10-mm thickness was placed in the middle of the ventricular part between the beginning and end of the left ventricle. The measurement of liver T2* was performed by imaging a single trans-axial slice (10-mmthickness) imaging in the liver. The normal T2* value was considered more than 20 ms with 95% confidence interval; signals of 14−20 ms indicated moderate amounts of iron overload, signals of 10−14 ms indicated average iron overload, and signals of < 10 indicated severe iron overload. Patients were divided into 4 categories based on evaluation of liver images: normal (> 6.3 ms), moderate (2.8−6.3 ms), intermediate (1.4−2.8 ms) and severe (< 1.4 ms) in terms of iron levels.

Statistical analysis

Descriptive statistics were first used to report information. Then, the Pearson correlation test was used to assess the relationship of ferritin and hemoglobin with heart and liver T2*MRI. A correlation coefficient of < 0.4 was considered to indicate weak, 0.4−0.6 intermediate, and > 0.6 strong correlation. All statistical analyses were conducted in SPSS software (IBM SPSS Statistics for Windows, version 22.0 Armonk, NY, USA). A p-value < 0.05 was considered to be significant.

Results

A total of 260 patients (mean age of 23-years-old) were enrolled in this study. The study included 228 patients with thalassemia major and 32 with thalassemia intermedia diagnostically. Clinical and demographic information of the patients is summarized in Table 1.

The average amount of hemoglobin and ferritin was 8.3 mg/dL and 2688 mg/mL. The average time of relaxation in the heart and liver was 11.7 and 3.86 ms, respectively. Iron increase was observed in 102 patients (39.2%), of which 45 patients (44.1%) had iron overload. In addition, the hepatic survey showed that 216 patients (83%) had increased iron deposition; among these, 75 patients (34%) had iron overload (Table 2). There were significantly more patients who were identified as having an iron overload based on the liver than based on the heart MRI data (Chi-square test, $p < 0.001$).

The hemoglobin levels did not show a significant correlation with T2* values of hepatic and cardiac MRI, while serum ferritin showed a strong, inverse correlation with T2* values in both heart ($r = -3.54$, $p < 0.0001$) and liver ($r = -3.03$, $p < 0.0001$) images (Table 2, Figs. 1, 2). A significant relationship ($r = 0.29$, $p < 0.0001$) was also observed between cardiac and hepatic T2* values (Fig. 3).

Table 1 Clinical and demographic characteristics of the patients

Characteristics		Major thalassemia $n = 228$	Intermediate thalassemia $n = 32$
Age		23.05	23.06
Sex	Male	104(45.6%)	11(34.4%)
	Female	124(54.4%)	65.6%)
Spleen	No palpitation	173(75.9%)	27(84.4)
	0-2 cm	13(5.7%)	0
	2-4 cm	10(4.4%)	1(3.1%)
	4-6 cm	11(4.8%)	0
	Up to 6 cm	21(9.1%)	4(12.5%)
	Splenectomy	95(41.7%)	17(53.1%)
Liver	Normal	205(89.9%)	30(93.8%)
	Less than 2 cm	4(1.8%)	1(3.1%)
	2-4 cm	7(3.1%)	0
	Up to 4 cm	12(5.3%)	1(3.1%)

Table 2 Pearson's correlation of hemoglobin, ferritin, and cardiac and hepatic T2* MRI results

MRIT2*	Hemoglobin	Pearson correlation	p value	Ferritin	Pearson correlation	p value
Heart		0.024	NS		–3.53	$p < 0.0001$
> 20 ms (158)	8.31			1988.32		
14-20 ms (30)	8.43			3075.07		
10-14 ms (27)	8.14			4861.33		
< 10 ms (45)	8.27			3584.62		
Liver		0.086	NS		–3.03	$p < 0.0001$
> 6.3 ms (44)	8.43			1099.12		
2.8-6.3 ms (52)	8.31			1471.69		
1.4- 2.8 ms (89)	8.15			3142.39		
< 1.4 ms (75)	8.38			3925.45		

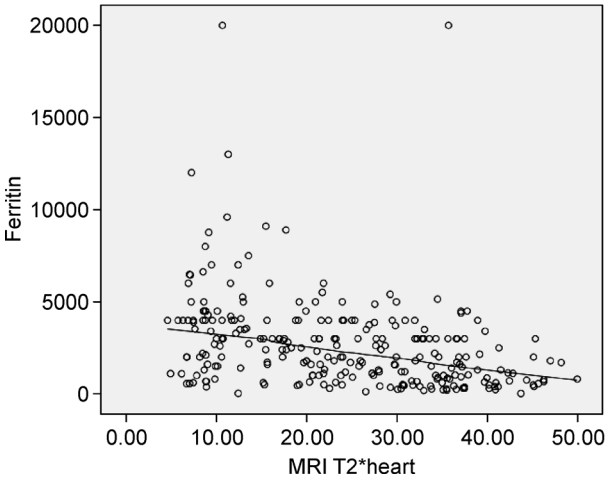

Figure 1 The relation between heart T2* MRI relaxation time and ferritin levels ($r = -3.54$, $p < 0.0001$)

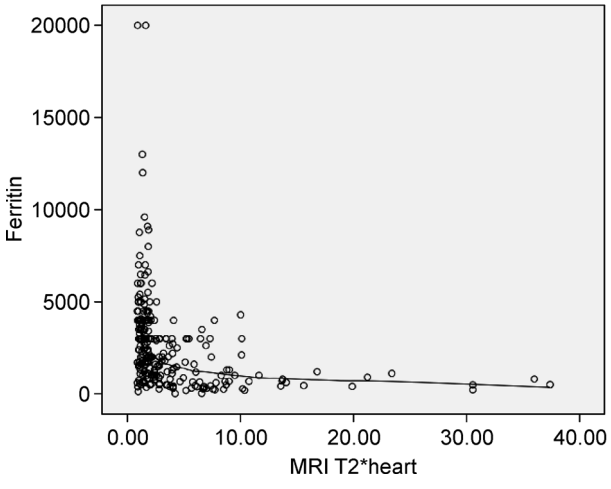

Figure 2 The relation between liver MRI T2* relaxation time and ferritin ($r = -3.03$, $p < 0.0001$)

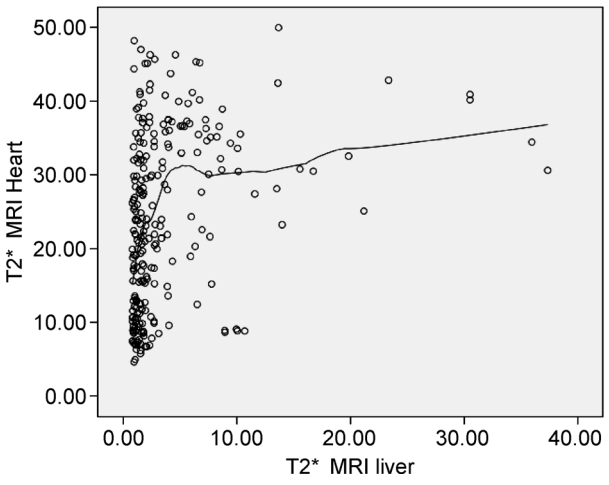

Figure 3 The relation between heart and liver T2* MRI relaxation time ($r = 0.29$, $p < 0.0001$).

Discussion

Accumulation of iron in various tissues is the most important complication in thalassemia patients receiving blood transfusions. Although iron-chelating therapies are used to control iron concentration, monitoring the concentration of tissue iron seems crucial. Iron levels have been evaluated by several methods, including measuring serum ferritin levels and by chemical examination of liver biopsy samples. Each of these methods has some disadvantages. Currently, the T2* MRI method has revolutionized the evaluation of tissue iron in thalassemia patients. It seems that this method can reflect the amount of iron in tissue well. For this reason, this study evaluated the relationship of ferritin and hemoglobin levels with liver and heart T2* MRI data, and determined the prevalence of iron overload in patients with thalassemia.

The results of this study indicated that approximately 39% of patients suffered from increased iron levels in the heart, of which 44% represented iron overload. Azarkeivan et al. (2016) also reported that 34% of patients had increased iron levels in the heart, and 32% of them had severe iron overload. Merchant *et al.* also proved that iron overload observed on MRI assessment of thalassemia patients was significantly increased as compared with healthy subjects. Assessment of the relationship between hemoglobin levels and cardiac T2* MRI results did not show any significant correlation. However, ferritin levels were strongly and inversely correlated with the results of T2* MRI of the heart. These findings agreed with those of other studies (Eghbali et al., 2014; Chen et al., 2015;Azarkeivan et al., 2016). However, Merchant et al. (2011)found no significant relationship between ferritin levels and cardiac T2* MRI data.

The results of cardiac MRI revealed that more than 80% of patients suffered from iron overload in the liver, and 34% of them showed severe iron overload. Further, assessing the relationship between the hemoglobin level with T2* MRI of liver showed no positive relationship, while the serum ferritin level showed strong inverse relationship with T2* MRI of liver. These findings were in line with those of other studies.

The results from heart and liver T2* MRI were directly correlated. Nevertheless, this was not confirmed by the study of Merchant et al. (2011). Azarkeivan et al. (2016) also showed a lack of relationship between liver and heart MRI in patients with thalassemia. However, in this study, the incidence of iron overload in the liver was significantly higher than that in the heart. These findings seem to suggest that cardiac iron overload follows that of the liver. The confirmation of this finding will require further studies.

Overall, the results of this study indicate that serum ferritin levels have a strong inverse relationship with T2* values of MRI of the liver and heart in patients with thalassemia. Therefore, T2* MRI can indicate body iron level in a non-invasive, highly accurate manner. The relatively high sample volume was an advantage, while the lack of investigation of other involved tissues, such as pancreas and kidneys, was a limitation of this study.

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Compliance with ethical standards

The authors declare that they have no conflicts of interest.

All procedures have been approved by the appropriate ethics committee and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent was obtained prior to intervention. Details that disclose the identity of the subjects under study were omitted.

References

Anderson L J, Holden S, Davis B, Prescott E, Charrier C C, Bunce N H, Firmin D N, Wonke B, Porter J, Walker J M, Pennell D J (2001). Cardiovascular T2-star ($T2^*$) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J, 22(23): 2171–2179

Azarkeivan A, Hashemieh M, Shirkavand A, Sheibani K (2016). Correlation between Heart, Liver and Pancreas Hemosiderosis Measured by MRI T2* among Thalassemia Major Patients from Iran. Arch Iran Med, 19(2): 96–100

Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini M D, Del Vecchio G C, Romeo M A, Forni G L, Gamberini M R, Ghilardi R, Piga A, Cnaan A (2004). Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine.

Haematologica, 89(10): 1187–1193

Cao A, Galanello R (2010). Beta-thalassemia. Genet Med, 12(2): 61–76

Chen X, Zhang Z, Zhong J, Yang Q, Yu T, Cheng Z, Chan Q, Guo H, Liang B (2015). MRI assessment of excess cardiac iron in thalassemia major: When to initiate? J MagnReson Imaging, 42(3): 737–745

Cunningham M J, Macklin E A, Neufeld E J, Cohen A R, and the Thalassemia Clinical Research Network (2004). Complications of beta-thalassemia major in North America. Blood, 104(1): 34–39

Eghbali A, Taherahmadi H, Shahbazi M, Bagheri B, Ebrahimi L (2014). Association between serum ferritin level, cardiac and hepatic T2-star MRI in patients with major β-thalassemia. Iran J Ped Hematol Oncol, 4(1): 17–21

Galanello R, Origa R (2010). Beta-thalassemia. Orphanet J Rare Dis, 5 (1): 11

Khosravi A, Jalali-Far M, Saki N, Hosseini H, Galehdari H, Kiani-Ghalesardi O, Paridar M, Azarkeivan A, Magaji-Hamid K (2016). Evaluation of α-Globin Gene Mutations Among Different Ethnic Groups in Khuzestan Province, Southwest Iran. Hemoglobin, 40(2): 113–117

Majd Z, Haghpanah S, Ajami G H, Matin S, Namazi H, Bardestani M, Karimi M (2015). Serum Ferritin Levels Correlation With Heart and Liver MRI and LIC in Patients With Transfusion-Dependent Thalassemia. Iran Red Crescent Med J, 17(4): e24959

Mazza P, Giua R, De Marco S, Bonetti M G, Amurri B, Masi C, Lazzari G, Rizzo C, Cervellera M, Peluso A, et al (1995). Iron overload in thalassemia: comparative analysis of magnetic resonance imaging, serum ferritin and iron content of the liver. Haematologica, 80(5): 398–404

Merchant R, Joshi A, Ahmed J, Krishnan P, Jankharia B (2011). Evaluation of cardiac iron load by cardiac magnetic resonance in thalassemia. Indian Pediatr, 48(9): 697–701

Ooi G C, Khong P L, Chan G C, Chan K N, Chan K L, Lam W, Ng I, Ha S Y (2004). Magnetic resonance screening of iron status in transfusion-dependent β-thalassaemia patients. Br J Haematol, 124 (3): 385–390

Rachmilewitz E A, Giardina P J (2011). How I treat thalassemia. Blood, 118(13): 3479–3488

Shabanian R, Heidari-Bateni G, Kocharian A, Mashayekhi M, Hosseinzadeh S, Kiani A, Izadyar M, Koochakzadeh L (2010). Augmentation of left atrial contractile function: a herald of iron overload in patients with beta thalassemia major. Pediatr Cardiol, 31 (5): 680–688

Wood J C, Fassler J D, Meade T (2004). Mimicking liver iron overload using liposomal ferritin preparations. Magn Reson Med, 51(3): 607–611

Alústiza J M, Emparanza J I, Castiella A, Casado A, Garrido A, Aldazábal P, San Vicente M, Garcia N, Asensio A B, Banales J, Salvador E (2015). Measurement of liver iron concentration by MRI is reproducible. Biomed Res Int, 2015:294024