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The Correlation between Serum Ferritin, Serum Troponin T, cardiac T2* MRI and Echocardiographic Findings in Patients with Thalassemia Major

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ABSTRACT

Background: Frequent blood transfusions lead to various complications in patients with thalassemia major. Heart problems caused by iron deposition in the myocardium are the major cause of death in patients with thalassemia major. Early diagnosis of cardiac dysfunction in patients with thalassemia major undergoing frequent blood transfusion is very important. We aimed to investigate the correlation between serum Ferritin level, serum Troponin T (TropT), cardiac T2* MRI and echocardiographic findings in patients with thalassemia major.

Methods: This cross-sectional study was conducted on all children >5 years old with thalassemia major admitted to Amirkabir Hospital, Arak, Iran, during 2016-2017. serum Ferritin level and Troponin T, echocardiography, and cardiac T2*MRI were analyzed in all participants.

Results: We found no correlation between serum ferritin and Trop T levels. However, there was a significant correlation between serum Trop T and serum ferritin with cardiac T2*MRI and also between serum Trop T and echocardiographic parameters (positive correlation with E/A ratio and functional shortening); and a negative correlation with left ventricular ejection fraction (LVEF). Moreover, there was no correlation between cardiac T2* MRI and echocardiographic findings.

Conclusion: Our results showed a positive correlation between serum troponin T with E/A size and FS and a negative correlation with LVEF and it was an important prognostic factor in early stage of cardiac damage in patients with thalassemia major. Moreover, there was a negative correlation between results of T2* MRI and serum ferritin and troponin T.

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Introduction

Thalassemia is a common hereditary anemia resulting from mutations in alpha or beta globin genes (1). Beta thalassemia major is the most severe form of thalassemia which causes ineffective erythropoiesis and anemia in the affected patients. The disease is prevalent in the Mediterranean countries, some parts of the North and the West of Africa, Middle East, India, and Southeast Asia (2, 3).

Patients with thalassemia major need regular blood transfusion to grow normally and improve their quality of life (4). Frequent blood transfusions lead to various

complications including infections, alloimmunization and excess iron deposits (5). After frequent transfusions, patients start to deposit iron in vital organs such as heart and liver (6). Although chelation therapy has been a routine and necessary treatment in the management of patients with thalassemia major since 1970, the major cause of death in patients is still heart disease due to iron deposition in the myocardium (7, 8). The cardiac complications in thalassemia major are mainly due to cardiac siderosis and include: conduction system impairment, dysfunction in cardiomyocytic contractility, delayed electrical conduction and increased electrophysiological heterogeneities (9-12).

There are several methods to estimate iron overload in the body. Serum ferritin level is a rough estimation of iron deposition in different organs. The main disadvantage of serum ferritin is that different conditions such as inflammation, infection, liver injury, and serum vitamin C levels could affect its levels (13). Cardiac T2* MRI is a recently applicable method for measuring iron overload in tissues which is useful to estimate the amount of the iron in the myocardium and liver. Cardiac T2* MRI in excess of 20 ms is considered as a normal speed range. Measures less than 10 ms are considered as serious iron overload and T2* MRI index less than 6 ms indicates very severe cardiac siderosis which means that the patient is at high risk of cardiac dysfunction (14, 15).

Troponin, or the troponin complex, is a complex of regulatory proteins integral to muscle contraction in skeletal and cardiac muscles, but not smooth muscles. Serum troponin is a cardiac biomarker of acute myocardial damage and is just measurable when the myocardial damage has occurred. The cardiac isoform of troponin T (cTnT) is a delicate filament made of skeletal and heart muscle contractile proteins. The cardiac subtype of troponin T is released into the blood-stream when damage to heart muscle occurs (16). Elevated serum troponin T is strongly related to cardiovascular mortality (17, 18). Troponin T increases even in the smallest cellular damage and is considered as a sensitive and specific marker in this regard. Heart failure is a progressive disease with difficulties in its management with a high mortality rate. Thus, early diagnosis, particularly in patients with thalassemia major is an essential part of the management of cardiac complications.

The present study was conducted to assess the correlation between serum ferritin and serum troponin T levels, cardiac T2* MRI and echocardiographic findings in patients with thalassemia major.

Patients and Methods

This descriptive cross-sectional study was conducted during 2016-2017 on 63 patients with thalassemia major older than 5 years old in Amirkabir Hospital, Arak, Iran. Written informed consent was obtained from patients or their parents. Ethical principles were observed and followed based on the ethical code approved by the Ethics Committee of Arak University of Medical Sciences (IR.ARAKMU.REC.1394.156). The exclusion criteria were presence of any simultaneous infection, renal failure, or congenital heart disease.

All patients were receiving regular blood transfusions with 3-4 week intervals to have hemoglobin level of 10 g/dl or higher. Patients received iron chelation therapy with deferiprone (DFP), deferrioxamine (DFO) or both. Demographic information including age, sex and age at first blood transfusion was obtained from the patient's records or through interview. Serum ferritin level was measured by Enzyme-linked immunosorbent (ELISA) (Awareness technology, US) and serum troponin T was measured by electrochemiluminescence immunoassay (ECLIA) in the same laboratory and at the same time.

Echocardiographic assessment was performed using a 3-8 MHz probe by ViVid 6 (GE Medical Systems, general electric, USA). Echocardiography was performed on the parasternal long axis and the apical four chambers. The ventricular function was evaluated using M-mode, pulsed-wave Doppler (PWD). We assessed echocardiographic parameters in five consecutive cardiac cycles to confirm the analysis (according to American society echocardiography). The PWD was assessed by placing the sample volume at 3-5 mm upper than the tip of the mitral valve. The results of left ventricular ejection fraction (LVEF) (%), Fractional Shortening (FS) (%) and E/Aratio (E: peak velocity blood flow in early diastole, A: peak velocity blood flow in late diastole caused by atrial contraction) were measured using the PWD method.

MRI was performed by Magneto Symphony Graniand 32, 1.5 Tesla (Siemens, Germany, 2003) in Noor Clinic (Tehran, Iran). Each scan lasted about 30 minutes and included the measurement of cardiac T2*. Cut-off points in this MRI instrument were as follows: normal >20 ms, mild: 14-20 ms, moderate: 10-14 ms, and severe <10 ms.

The data were reported as mean±SD (at a significant level of $P<0.05$). Linear regression and other descriptive statistical tests were used to compare the variables. The analyses were performed in SPSS software, Version 22 (SPSS Inc, Chicago, IL, USA).

Results

Sixty- three patients were assessed in this study. The mean±SD age of the patients was 23.19±9.86 years old (range: 5 to 54 years), and 29 (46%) patients were male. Mean±SD age at start of transfusion was 1.1±0.8 years. Mean±SD serum troponin T and ferritin levels were 1.15±0.18 (pg/ml) and 2694.7±1894.9 (ng/ml), respectively. The mean±SD T2*MRI was 23.58±8.21 ms (range: 8.36-45.8 ms). Mean±SD E/Aratio, FS and LVEF were 2.63, 35.96 (%), and 60.51 (%), respectively (Table 1).

There was no correlation between serum ferritin and troponin T levels (Table 2). There was a negative correlation between T2* MRI index and serum ferritin and troponin T levels (R=-0.41 and -0.287, respectively) and also between LVEF and serum troponin T level (R=-0.530) (Table 3).

By comparing the correlations between E/A ratio and FS with serum troponin T, the hypothesis of the independent variables was rejected ($P<0.005$) and there was a positive correlation between the variables (R=0.41 and 0.958, respectively) which means that E/A ratio and FS increased

Table 1: Serum Troponin T, serum Ferritin, echocardiographic parameters and T2* MRI in patients with Thalassemiamajor

	Mean	Standard deviation	Minimum	Maximum
Troponin T	0.18	1.15	0.0	9.2
Ferritin	1894.9	2655.7	2	16000
E/A	2.63	5.23	1.07	42
FS	35.96	9.16	19	67
LVEF	60.51	10.9	20.54	80
T2*MRI	23.58	8.21	6.76	38.30

LVEF: Left ventricular ejection fraction, FS: Fractional Shortening, E/Aratio:peak velocity blood flow in early diastole/ peak velocity flow in late diastole

Table 2: Correlation between serum troponin T and ferritin levels in patients with thalassemia major

	Mean	Standard deviation	P value	Pearson correlation
Troponin T	0.18	1.15	0.67	-0.054
Ferritin	1894.9	2655.7	0.67	-0.054

Table 3: Correlation of T2* MRI index with serum ferritin and troponin T and serum troponin T with LVEF in patients with thalassemia major

	Mean	Standard deviation	P value	Pearson correlation
T2* MR	23.58	8.21	0.001	-0.411
Ferritin	1894.9	2655.7		
T2* MR	23.58	8.21	0.023	-0.287
Troponin T	0.18	1.15		
Troponin T	0.18	1.15	0.00	-0.530
LVEF	60.51	10.09		

Table 4: Correlation of serum Troponin T with E/A ratio and FS in patients with thalassemia major

	Mean	Standard deviation	P value	Pearson correlation
Troponin T	0.18	1.15	<0.005	0.41
E/A ratio	2.63	5.23		
Troponin T	0.18	1.15	0.023	-0.287
FS	35.96	9.16		

Table 5: Correlation of T2* MRIwith E/A, FS and LVEF and serum ferritin with E/A ratio in patients with thalassemia major

	Mean	Standard deviation	P value	Pearson correlation
T2* MRI	85.32	8.21	0.058	-0.240
E/A ratio	2.63	5.23		
T2* MRI	23.58	8.21	0.812	0.031
FS	35.96	9.16		
T2* MRI	23.58	8.21	0.15	0.183
LVEF	60.51	10.9		
Serum ferritin	1894.9	2655.7	0.34	-0.122
E/A ratio	2.63	5.23		

as serum troponin T levels increased (Table 4).

Based on the comparison of correlations between T2 * MRI, FS, LVEF and serum ferritin with E/A, the hypothesis of the independent variables was also rejected (P>0.05) which showed that there was no correlation between the above mentioned variables (Table 5).

Discussion

We found no correlation between serum troponin T and ferritin levels in patients with thalassemia major which was consistent with another study in such patients (19). It is assumed that due to delay in developing symptoms and echocardiographic abnormalities, early diagnosis of heart involvement in thalassemia major sounds challenging and an early marker such as troponin T is needed to be capable of early diagnosis of cardiac disease.

The results of our study showed a negative correlation between T2* MRI index and serum ferritin levels in patients with thalassemia major which means that while serum ferritin level was increasing, T2* MRI index was decreasing. In a study on 63 patients with thalassemia major, no significant relationship between serum ferritin levels and cardiac function indexes in echocardiography was found, but T2*MRI results showed a significant negative correlation with serum ferritin level (patients with ferrtin levels >2000 ng/ml had abnormal cardiac MRI indexes) (20). It seems that serum troponin T level might not be entirely specific or sensitive for evaluating cardiac function in patients with thalassemia major. As a result, cardiac T2*MRI is already used to detect cardiac dysfunction in patients with thalassemia major.

Akcay and colleagues evaluated 64 patients with

thalassemia major. There was no significant correlation between serum levels of ferritin and cardiac T2* MRI (21). The differences in the above studies could be explained by the ethnic differences of the patients and the sample size or methodology of the studies. In another study, there was also a negative correlation between serum ferritin level and T2* MRI index; however, the correlation was not significant (22).

Our study showed a positive correlation between serum troponin T levels and E/A ratio. E/A ratio increased with increasing trend in serum troponin T levels. Moreover, there was a positive correlation between serum troponin T and FS in echocardiography.

The role of troponin I as a specific marker for cardiac injury in 60 patients with thalassemia major was evaluated and they found no correlation between Troponin I level and cardiac function in these patients (23). In our study, serum levels of troponin T indicated a negative correlation with LVEF and positive correlation with E/A rtio and FS. our study showed that increased troponin T may indicate cardiac involvement in patients with thalassemia major.

Another study indicated that serum troponin T levels were significantly higher in patients with diastolic dysfunction of the left ventricle (24). Their study however was not performed necessarily in patients with thalassemia. Another study in a group of non-thalassemic patients also showed a negative correlation between LVEF and serum troponin T levels (25).

Conclusion

Our results showed a positive corelation between serum troponin T with E/A ratio and FS and a negative correlation with LVEF and it was an important prognostic factor in early stage of cardiac damage in patients with thalassemia major. Moreover, there was a negative correlation between T2* MRI index and serum ferritin and troponin T levels.

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Conflict of Interest: None declared.

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