Parameters of tissue iron overload and cardiac function in patients with thalassemia major and intermedia

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Abstract

Background: Noninvasive T2* magnetic resonance imaging (MRI) assessment can stratify the risk of subsequent cardiac dysfunction in β-thalassemia major (TM) and β-thalassemia intermedia (TI) patients. The normal level of N-terminal pro B-type natriuretic peptides (NT-proBNP) can rule out acute heart failure. Aim: We aim to investigate the relation of NT-proBNP level, T2* MRI, and echocardiographic findings in TM and TI patients. Materials and methods: In this cross-sectional study, 41 TM patients, 41 TI patients, and 41 healthy individuals (HI) were enrolled. NT-proBNP level, T2* MRI, and two-dimensional echocardiography were assessed for all patients and controls. Results: There was statistically significant correlation between NT-proBNP levels and mitral inflow late diastolic velocity ($r = -0.538$; $p = 0.006$) in TM group. There was statistically significant correlation between NT-proBNP levels and tricuspid annulus systolic velocity ($r = -0.438$; $p = 0.028$), systolic velocity of septum ($r = -0.472$; $p = 0.020$), and mitral inflow early-to-late diastolic wave ratio ($r = 0.592$; $p = 0.002$) in TM group. Conclusion: Early diagnosis and treatment of myocardial iron overload are likely to prevent the mortality in patients with established ventricular dysfunction. Since NT-proBNP levels were not significantly increased in documented left ventricular (LV) diastolic dysfunction, this factor may not be sensitive for the detection of latent LV diastolic dysfunction in the early stages of disease progression.

Introduction

Impaired synthesis of β-globin chain is called β-thalassemia, which is widely spread through the Mediterranean area, Africa, and the Middle East [1]. Chronic blood transfusions improve oxygen delivery, suppress ineffective erythropoiesis, and prolong survival, but the predictable side effect is particularly iron overload [1, 2].

Patients with β-thalassemia intermedia (TI) display similar stigmata of ineffective erythropoiesis, but they survive without regular transfusion. Tissue iron overload is secondary to excess gastrointestinal absorption due to accelerated erythropoiesis [1, 2, 3].

Tissue iron overload, as the most important complication, causes organ damage which is fatal if not prevented or effectively treated; thus, it can be a major focus of management [4]. The leading cause of death is cardiac iron overload in patients with β-thalassemia major (TM) and TI, which is associated with cardiac dysfunction and also usually with chronic cardiac failure [4, 5].

Serum ferritin assay is a simple way for evaluating cardiac risk; this inexpensive widely available measurement has also limited usefulness in iron load assessment [5–9]. Cardiac iron uptake and toxicity may occur despite apparently adequate total body iron balance [10, 11, 12]. Electrocardiography and echocardiography signs of toxicity do not appear until severe cardiac iron deposition has occurred [9, 13].

Cardiac toxicity is often insidious; less than half of the patients with β-thalassemia have detectable cardiac iron, though many of them are asymptomatic [14, 15].

Noninvasive T2* magnetic resonance imaging (MRI) assessment can reliably detect subclinical cardiac iron concentrations and can predict the risk of subsequent cardiac dysfunction [10, 13]. Cardiac T2* MRI hopefully provides a longer treatment window for iron overload-induced cardiomyopathy. It is also possible to identify early onset systolic dysfunction and intensive chelation requirement and prevention of mortality associated with overt heart failure [10, 16, 17, 18].

N-terminal pro B-type natriuretic peptide (NT-proBNP) is secreted by the heart ventricles in response to excessive stretching of cardiomyocyte, which decreases blood pressure due to the reduction in systemic vascular resistance [19, 20]. Both B-type natriuretic peptide (BNP) and NT-proBNP levels are also typically increased in left ventricular (LV) dysfunction with or without symptoms [21]. They have developed as sensitive biomarkers for screening, diagnosis, treatment, and prognosis of heart failure [22, 23, 24]. These biomarkers levels are significantly increased in obvious LV diastolic dysfunction, while NT-proBNP level seems to have better predictive value in detecting latent LV diastolic dysfunction in TM patients [25, 26, 27].

Survival of β-thalassemia patients with heart failure can be dramatically improved by early diagnosis of LV diastolic dysfunction and

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intensification of iron chelation therapy. Thus, we decided to investigate the association of NT-proBNP level with echocardiographic findings of asymptomatic LV diastolic dysfunction, T2* MRI's subclinical cardiac iron concentrations assessment, and serum ferritin level.

Patients and methods

Study design and patients

This is a cross-sectional case–control study on TM and TI patients, who had been registered in thalassemia ward, affiliated to Shiraz University of Medical Sciences, from January 2015 to December 2015. We enrolled 41 TM patients who had been under regular follow-up and received regular blood transfusion every 3–4 weeks before the age of 2 in order to maintain the hemoglobin levels above 9.5 g/dL. All patients received iron chelation therapy before the age of 4. In addition, 41 TI patients who have occasionally transfused and under regular follow-up were enrolled in this study. Only 15 patients (33%) from TI group were under regular iron chelation therapy.

Furthermore, all enrolled patients had clinical and hematological data records including regular vital signs and growth measurements, duration and types of iron chelator, regular cardiovascular assessment such as cardiologist consultation, and echocardiography.

Similarly, 41 healthy individuals (HI) as control group without positive history of cardiovascular disease and clinical or paraclinical cardiovascular evidence were randomly selected from day clinic visitors. This study protocol was approved by the institutional ethics committee and all enrolled patients and/or guardians signed written informed consent.

Clinical and biochemical variables

We recorded mean of hemoglobin level during last 6 months, mean serum ferritin level in last year, the latest renal function tests (blood urea nitrogen and creatinine), liver function tests (alanine aminotransferase, aspartate transaminase, alkaline phosphatase, albumin, total bilirubin, and direct bilirubin), uric acid of case groups (TM and TI patients), and serum level of NT-proBNP of cases (TM and TI patients) and control groups.

NT-proBNP measurements were performed with Siemens competitive enzyme immunoassay kit (Siemens healthcare diagnostics, Marburg, Germany). As a general guideline, 90% of young healthy adults have NT-proBNP < 70 pg/mL [28].

T2* MRI

T2* MRI was performed by Siemens 1.5 Tesla (T) MRI (Siemens Healthcare GmbH, Germany). Result showing > 20 ms indicates no significant iron loading, 10–19 ms indicates mild-to-moderate iron loading, and < 10 ms indicates severe cardiac iron loading associated with severe LV dysfunction [10].

Echocardiography mode

Echocardiography was performed by Mindray DC7 (China, Shanghai) echocardiography machine using a 3 MHz probe. To evaluate systolic and diastolic functions, all M-mode, two-dimensional (2D), Doppler, and pulse tissue Doppler echocardiographic measures were performed by a cardiologist in left lateral decubitus position.

Statistical analysis

All tests were performed using SPSS 21 software package (SPSS, Chicago, IL). Data were presented as mean, standard deviation, and percentage. Normality of data was checked by Kolmogorov-Smirnov test. Comparison of continuous variables between the three groups was determined by Student's t-test and Mann-Whitney U test as appropriate. Chi-squared test was used to compare qualitative variables between two or more groups of patients. One-way analysis of variance (ANOVA) was used to assess the differences among ≥ 3 consecutive groups, and post hoc adjustments for multiple comparisons were assessed using Bonferroni's method. Correlation of NT-proBNP with quantitative parameters was estimated using Pearson correlation test. The p-value < 0.05 was considered to be statistically significant.

Result

Clinical and laboratory findings

Mean age of the patients was 26.3 ± 7.5 years (ranged 8–40 years) including 35 females and 6 males in TM group, 21 females and 20 males in TI group, and mean age of HI group was 28.6 ± 11.6 (ranged 8–35 years) including 8 females and 33 males. There were no significant age differences among the three groups (p > 0.05).

The highest mean serum ferritin level was found in TM, then TI, and the least in HI with significant difference between groups (p < 0.001, Tab. I). The mean serum NT-proBNP level in all group was in

Table I. The mean of ferritin, T2*MRI, and NT-proBNP in TI, TM, and HI groups

Parameters (N)	Mean ± SD	95% CI
		Lower–Upper
Ferritin		
TI (37)	403.7 ± 273.7	322.9–490.9
TM (41)	2141.2 ± 1922.1	1658.5–2840
HI (14)	86.8 ± 28.2	71.6–101.4
Total (92)	1129.8 ± 1580	834.2–1496.8
T2* MRI		
TI (33)	33.1 ± 12.5	29.3–37.9
TM (38)	25.4 ± 14.7	21.0–30.2
HI (ND)	ND	ND
Total (71)	29 ± 14.1	26 ± 32.4
NT-proBNP		
TI (40)	45.8 ± 61.6	20.1–101.1
TM (39)	17.8 ± 17.1	13.9–24.2
HI (14)	12.9 ± 1.7	12–13.9
Total (93)	29.1 ± 44.1	21.5–39.6

ND – not done; TI – β-thalassemia intermedia; TM – β-thalassemia major; HI – healthy individual

normal range, but the highest was found in TI group with significant difference between two other groups (TM and HI) (p = 0.008, Tab. I). No statistical difference was detected between TM and HI groups. Only three patients in TI group had NT-proBNP > 70 pg/mL.

Echocardiographic parameters

Mean of ejection fraction (EF) was not different in three groups (EF in TM: 71%, EF in TI: 70%, and EF in HI: 71%; p = 0.8). Five patients had systolic dysfunction (EF < 55%), four patients in TM group, and one patient in TI group. None of these cases had T2* MRI < 20 or high NT-proBNP level.

TI group had statistically higher mean values for LV internal dimension in diastole (LVIDd), end diastolic LV volume (EDV), LV internal dimension in systole (LVIDs), and stroke volume (SV) rather than other two groups (TM and control have no difference in M-mode data) (Tab. II). Interestingly, abnormal LVIDd that indicated dilated LV (LVIDd > 5.6) had the highest prevalence in TI group (8 cases out of total 9 cases).

The group with high LVIDd (LVIDd > 5.6) had higher NT-proBNP level (79.7 vs. 20.4 with p < 0.001) but not statistically different ferritin level (p = 0.06). Results of T* MRI were >20 ms in both groups with borderline difference (34.2 in high LVIDd vs 28.4 in normal LVIDd, p = 0.043).

Diastolic function evaluation

No statistically difference was seen between three groups in mean of E/A ratio (p = 0.51) or E_{aM}/A_{aM} (p = 0.38). Based on mitral inflow, Doppler finding (5.6%) showed reverse E/A ratio in only three patients and four patients (7.4%) showed E/A ratio > 2. Data of Date of tissue Doppler imaging (TDI) showed more diastolic impairment (20.8% reverse E_{aM}/A_{aM} ratio). None of the patients had restrictive pattern in Doppler plus TDI finding or based on E/E_a ratio > 15. Due to low number of diastolic impairment, comparison between different groups was not meaningful.

Correlation analysis

Between biochemical marker and echocardiographic finding, only NT-proBNP had correlation with LVIDd (r = 0.415, p = 0.002) and EDV (r = 0.458, p = 0.001). Ferritin has no correlation with echocardiographic finding (Tab. III). T2* MRI had weak reverse correlation with ferritin level (r = -0.384, p = 0.001). Interestingly, T2* MRI has no correlation with the result of echocardiographic finding, 2D and Doppler index, and TDI (Tab. III).

Iron overload state

In TM group, 39.5% had iron overloading (T2* MRI < 20 ms) vs. 6.1% of TI group. Serum ferritin was statistically different between these groups with cardiac iron load studied using MRI (ferritin level: 4217 ± 2177, 2280 ± 2569, and 920 ± 912 for severe, mild, and no iron load, respectively; p = 0.001) (Tab. IV). Other factors such as age, NT-proBNP level, and echocardiographic data were not different in these groups with cardiac iron loading.

Table II. Descriptive values and comparison of echocardiographic findings in TI, TM, and HI groups

Parameters		N	Mean ± SD	p
IVSd	TI	18	1.0 ± 0.19	
	TM	22	1.0 ± 0.32	
	HI	14	1.2 ± 0.22	0.209
	Total	54	1.1 ± 0.26	
LVIDd	TI	18	5.6 ± 0.61	
	TM	22	4.8 ± 0.57	
	HI	14	4.5 ± 0.48	<0.001
	Total	54	5.0 ± 0.71	
LVPWd	TI	18	1.0 ± 0.18	
	TM	22	0.9 ± 0.27	
	HI	14	0.98 ± 0.21	0.368
	Total	54	0.96 ± 0.23	
EDV	TI	18	157.2 ± 39.3	
	TM	22	110.9 ± 28.8	
	HI	14	95.7 ± 23.9	<0.001
	Total	54	122.3 ± 40.2	
IVSs	TI	18	1.4 ± 0.24	
	TM	22	1.3 ± 0.21	
	HI	14	1.5 ± 0.37	0.378
	Total	54	1.4 ± 0.27	
LVIDs	TI	18	3.2 ± 0.47	
	TM	22	2.8 ± 0.67	
	HI	14	2.6 ± 0.51	0.007
	Total	54	2.9 ± 0.61	
LVPWs	TI	18	1.2 ± 0.22	
	TM	22	1.0 ± 0.25	
	HI	14	1.2 ± 0.22	0.321
	Total	54	1.1 ± 0.24	
ESV	TI	18	265.8 ± 937.7	
	TM	22	33.2 ± 19.6	
	HI	14	26.6 ± 12.1	0.330
	Total	54	109.0 ± 542.9	
SV	TI	18	112.5 ± 29.7	
	TM	22	77.7 ± 19.4	
	HI	14	69.0 ± 18.4	<0.001
	Total	54	87.0 ± 29.3	
EF	TI	18	70.1 ± 10.4	
	TM	22	71.5 ± 11.3	
	HI	14	72.4 ± 9.9	0.835
	Total	54	71.3 ± 10.55	

IVSs – interventricular septal thickness in systole; LVIDd – left Ventricular Internal dimension in diastole; EDV – end-diastolic left ventricular volume; IVSd – interventricular septal thickness in diastole; LVIDs – left ventricular internal dimension in systole; LVPWd – left ventricular posterior wall thickness in diastole; LVPWs – left ventricular posterior wall thickness in systole; ESV – end systolic left ventricular volume; SV – stroke volume; EF – ejection fraction; FS – fractional shortening

Table III. Correlation analysis between biochemical marker and echocardiographic findings

Parameters		Ferritin	T2* MRI	NT-proBNP	LVIDd	EDV	ESV	E/A ratio mitral	E_a/A_a ratio
Ferritin	Pearson	1	-0.368**	-0.099	0.154	0.130	0.038	0.113	0.043
	P		0.002	0.355	0.270	0.352	0.788	0.418	0.758
	N	92	70	89	53	53	53	54	53
T2* MRI	Pearson	-0.368**	1	0.111	0.193	0.185	0.093	0.315	-0.044
	P	0.002		0.366	0.267	0.287	0.597	0.061	0.804
	N	70	71	68	35	35	35	36	35
NT-proBNP	Pearson	-0.099	0.111	1	0.415**	0.458**	0.026	-0.115	-0.062
	P	0.355	0.366		0.002	0.001	0.853	0.408	0.658
	N	89	68	93	53	53	53	54	53
LVIDd	Pearson	0.154	0.193	0.415**	1	0.994**	0.094	0.027	-0.124
	P	0.270	0.267	0.002		0.000	0.500	0.847	0.377
	N	53	35	53	54	54	54	54	53
EDV	Pearson	0.130	0.185	0.458**	0.994**	1	0.083	0.012	-0.141
	P	0.352	0.287	0.001	0.000		0.548	0.933	0.313
	N	53	35	53	54	54	54	54	53
ESV	Pearson	0.038	0.093	0.026	0.094	0.083	1	0.093	0.358**
	P	0.788	0.597	0.853	0.500	0.548		0.502	0.009
	N	53	35	53	54	54	54	54	53
E/A ratio mitral	Pearson	0.113	0.315	-0.115	0.027	0.012	0.093	1	0.076
	P	0.418	0.061	0.408	0.847	0.933	0.502		0.586
	N	54	36	54	54	54	54	55	54
Ea/Aa ratio	Pearson	0.043	-0.044	-0.062	-0.124	-0.141	0.358**	0.076	1
	P	0.758	0.804	0.658	0.377	0.313	0.009	0.586	
	N	53	35	53	53	53	53	54	54

**Correlation is significant at the 0.01 level (two-tailed); NT-proBNP – N-terminal pro B-type natriuretic peptide; LVIDd – left Ventricular Internal; dimension in diastole; EDV – end-diastolic left ventricular volume; ESV – end-systolic left ventricular volume

Table IV. Ferritin, age, NT-proBNP level, and echocardiographic data in different categories of iron overload according to T2 MRI*

Parameters	T2* MRI category	N	95% confidence interval for mean		P
			Lower bound	Upper bound	
Ferritin	< 10 ms	6	1932.5	6502.1	0.001
	≥ 10 ms and < 20 ms	11	553.8	4006.6	
	≥ 20 ms	53	668.9	1172.0	
	Total	70	1009.4	1824.1	
NT-proBNP	< 10 ms	6	-15.9	74.3	0.972
	≥ 10 ms and < 20 ms	10	9.1	44.7	
	≥ 20 ms	52	22.0	36.2	
	Total	68	22.3	35.2	
EF	< 10 ms	2	29.5	121.0	0.127
	≥ 10 ms and < 20 ms	6	75.4	84.3	
	≥ 20 ms	27	66.6	75.0	
	Total	35	69.1	76.1	
EDV	< 10 ms	2	37.9	249.2	0.255
	≥ 10 ms and < 20 ms	6	71.5	137.4	
	≥ 20 ms	27	116.6	149.6	
	Total	35	115.0	142.6	
Age	< 10 ms	6	23.3	31.2	0.920
	≥ 10 ms and < 20 ms	11	20.3	31.3	
	≥ 20 ms	54	24.2	28.3	
	Total	71	24.5	28.0	
E/A ratio mitral	< 10 ms	2	-0.09	2.95	0.802
	≥ 10 ms and < 20 ms	7	0.98	1.73	
	≥ 20 ms	27	1.30	1.65	
	Total	36	1.30	1.59	
Ea/Aa ratio	< 10 ms	2	-3.62	6.27	0.542
	≥ 10 ms and < 20 ms	7	1.38	2.18	
	≥ 20 ms	26	1.44	1.88	
	Total	35	1.49	1.84	

NT-proBNP – N-terminal pro B-type natriuretic peptide; EF – ejection fraction; EDV – end-diastolic left ventricular volume

Discussion

This is a cross-sectional study on patients with β-thalassemia syndrome and age and gender-matched healthy controls. In this study, the NT-proBNP and serum ferritin levels, systolic and diastolic functions of the LV on standard Doppler and pulsed Doppler tissue imaging, and T2* MRI results in β-thalassemia patients were compared with each other and with HI.

In this study, serum ferritin level was significantly higher in the TM group compared with TI and HI groups, and statistically significant between patients and HI group. Higher ferritin level was due to suboptimal chelation therapy in these patients [29]. Our study showed more advance iron loading class in cardiac MRI associated with higher level of serum ferritin although there is no linear correlation with cardiac MRI index and serum ferritin. This study also showed that biochemical markers (ferritin and NT-proBNP) are weak indicators of iron loading state and they cannot predict level of iron loading. NT-proBNP has weak correlation with cardiac MRI index but it cannot predict iron overloading even in severe case of cardiac iron overload (mean NT-proBNP 29.1, 26.9, and 29.1 for severe, mild, and no iron load in T2* MRI; p = 0.9) and should not be used as a marker of cardiac iron load.

Systolic function is a nonsensitive and nonspecific marker of cardiac iron loading which was confirmed in this study and other studies. Even severe iron loading (T2* MRI < 10 ms) may be present with good LV systolic function, iron overload appears to mediate the impaired diastolic function leading to stiffness of the myocardial wall but LV systolic function preserves normal [29]. Diastolic dysfunction was not common in this study and we had no correlation between cardiac iron state and echocardiographic diastolic function parameters. It seems that these parameters are not sensitive to detect iron overloading (only one of diastolic dysfunction cases had abnormal T2*MRI). Therefore, echocardiography is neither sensitive nor specific for diagnosis of cardiac iron overload state.

In this study, most of the cases with abnormal cardiac iron load belong to TM group (88% of all cases with cardiac MRI < 20 ms). This group had highest ferritin level but interestingly they had better echocardiographic marker than TI group. In addition to less serum ferritin in TI, these patients had more LV dilation (44% in TI vs. 4% in TM) and LV diastolic dysfunction was more common in TI group (16.6% in TI vs. 9% in TM).

The end diastolic LV volume, diastolic interventricular septal thickness, the LV posterior wall thickness, SV, and the end systolic volume were statistically higher in TI group compared with TM and HI groups. All of these indices, which are indicative of increased cardiac load, may affect chronic anemia in TI paxtients. Similar observations by Amoozgar et al. showed that peak systolic velocity of the posterior wall was significantly higher in TI compared with controls (p < 0.05) [30].

The tricuspid inflow diastolic and mitral wave velocities were significantly higher in TI group. Compared with TM and HI groups, the LV diastolic indices of TI showed higher early LV diastolic filling, and higher E/A ratio in TM suggested restrictive diastolic pattern and stiff myocardial wall. These findings are confirmed from the study by Yaprak et al. [31].

Tissue Doppler study showed that the mitral annulus systolic velocity was statistically significant between TI and HI groups. The mitral annulus early diastolic velocity was significantly higher in thalassemia patients. The mitral annulus late diastolic velocity was significantly higher in TI but the study by Amoozgar et al. showed that pulse tissue Doppler of the lateral mitral annulus had not significantly changed in TI compared with control [30].

The systolic velocity of septum was significantly higher in TI group compared with TM and HI, which may be due to the effect of chronic anemia on intermedia patients. Higher and statistically significant tricuspid annulus systolic velocity and inflow early and late diastolic velocity in β-thalassemia patients compared with control indicated anemia and hyperdynamic state. The findings by Amoozgar et al. [30] showed that the peak systolic velocity of the septum and the tricuspid annulus had increased significantly in TI patients.

The mean serum NT-proBNP level, as an indicator of asymptomatic LV dysfunction, was higher in thalassemia group than control group. However, there was near to statistically significant difference between TI and control, and statistically significant differences also exist between TI and TM groups which may be due to the effect of irregular transfusion on increased cardiac volume and pressure overload in TI patients. Özyörük et al. [32] and Eghbali et al. [33] found that NT-proBNP levels were significantly higher in thalassemia patients in comparison with normal subjects.

In this study, the serum level of proBNP in TM and TI in the absence of overt heart failure was normal with no correlation with E/E_{am} ratio, but in a report by Kremastinos et al. [34] patients with TM with no heart failure had higher NT-proBNP and E/E_{am} ratio compared with controls with positive correlation between both variables. It was also found that NT-proBNP serum level significantly increased in patients with documented LV diastolic dysfunction [34]. This difference between studies may be due to better chronic care in our patients.

We found that cardiac T2*MRI did not have statistically significant relationship with serum ferritin or NT-proBNP level, although there was significant difference between β-thalassemia patients and control group. This may indicate that iron status is an unreliable parameter for management of cardiologic complication in β-thalassemia patients. Similar observations were reported by Anderson et al. [10]. We may need a large cohort of β-thalassemia patients to study carefully and closely the relationship between cardiac T2* MRI and serum NT-proBNP level.

Although we could not find significant correlation between M-mode and T2* MRI index in TM and TI, correlation between cardiac T2* MRI and Doppler echocardiography indices in TI may be explained by the effect of irregular transfusion in TI patients which affects LV function. Although mean serum proBNP level was higher in TI compared with TM and control groups, myocardial iron content cannot be predicted from serum proBNP. Early diagnosis and treatment of myocardial iron overload is likely to prevent the mortality in patients with established ventricular dysfunction.

Since proBNP levels were not significantly increased in documented LV diastolic dysfunction, this factor may not be sensitive for detection of latent LV diastolic dysfunction in early stages of disease progression.

Authors' contributions

SS, NSH, SH, HA, and MK – paper design. SS, SS, HM, and ORZ – manuscript writing. All authors – revision of manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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