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Evaluation of the relationship between hepatic and cardiac iron overload with MRI T2* and carotid intima media thickness with Doppler ultrasound in beta thalassemia major patients

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Abstract

Background: Iron overload is caused early progression of atherosclerosis in beta thalassemia patients due to regular repeated blood transfusion. MRI T2* is a gold standard non-invasive method for detecting hepatic and cardiac iron overload. The aim of this study was the comparison of carotid intima media thickness (CIMT) in the patients and healthy control groups with Doppler ultrasound for early diagnosis of atherogenesis. Another purpose was to assess the relationship between CIMT and iron overload among patients.

Materials and methods: This cross-sectional study was performed on twenty patients referred to the Sarvar clinic and twenty age- and sex-matched control group. The CIMT was measured with Color Doppler ultrasound in both groups. Then, MRI T2* results, demographic, and therapeutic information were extracted from their documents.

Results: CIMT was insignificantly higher in the patients compared to the control group. For example, it was 0.49 ± 0.05 vs. 0.45 ± 0.03 (p = 0.009) for the right common carotid artery (RCCA) and 0.48 ± 0.06 vs. 0.46 ± 0.04 (p = 0.17) for the left common carotid artery (LCCA). There was no strong relationship between CIMT and age (p = 0.09 for RCCA, p = 0.00 for LCCA), sex, chelation type (for example, p = 0.51 for RCCA with Desferal and p = 0.91 for LCCA with Desferal), age at diagnosis, age at the beginning on transfusion (p = 0.49 for RCCA, p = 0.20 for LCCA), age at the start of chelator (p = 0.74 for RCCA, p = 0.78 for LCCA), and hepatic and cardiac iron overload.

Conclusion: Preventive and curative methods should be planned to cease its progression. Furthermore, early initiation of chelator drugs with better efficacy and compliance may reverse the hepatotoxic and adverse myocardial effects of excessive iron.

Key words: Beta thalassemia major; Carotid intima media thickness; Iron overload; Magnetic Resonance Imaging

Introduction

Thalassemia major is an autosomal recessive inherited disease. Every year, one hundred thousand infected neonates are born all over the world (1). In beta thalassemia (BT), a genetic defect in a gene related to hemoglobin is happening because of decreasing beta chain synthesis. The excess production of alpha chain (relative to beta) is resulted in precipitation of alpha chain in hemoglobin A. Consequently, inclusion of body and hemolytic anemia is occurred (1-5). Hemolysis would be occurred due to ineffective erythropoesis in thalassemia patients (1). The common treatment for BT major is regular repeated blood transfusion (1-3,6). Transfusion in association with ineffective erythropoesis and excessive absorption of iron from gastrointestinal tract is resulted in secondary hemosidrosis.

Iron overload is started to precipitate in reticuloendothelial system initially and in other parenchymal organs, specially heart, pancreas, hypophysis, and gonads accordingly (1,3-7). Excess iron builds up the heart, liver, joints, pancreas, and pituitary gland. If it remains untreated, it can cause organ damage and lead to heart attack, diabetes, cirrhosis, arthritis, depression, and premature death (8). Early chelation therapy prevents accumulation of iron in tissues of BT major patients and reduces the adverse effects of iron overload in different organs (9-11). Iron chelators

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normalize the endothelial function and decrease cardiovascular events risk. These drugs prevent the early atherosclerotic changes (12). Currently, there are three iron chelators for curing BT disease: 1) Deferiprone (Ferriprox, DFP), 2) Deferasirox (Exjade, DFX), 3) Deferoxamine (Desferal, DFO) (7). Beta thalassemia patients receive chelators as monotherapy or combined therapy (13). DFP and DFX are preferentially used as oral treatment, because of better compliance and easy usage (7).

Magnetic resonance imaging (MRI) is a non-invasive and reliable method for iron overload measurement (3,4,6,14-16). Recent progression in the field of MRI provides more sensitive and meticulous tool than using ferritin for evaluating iron overload in different tissues, such as liver, heart, and endocrine glands (3,16,17). T2* technique is a gold standard for detecting myocardial iron overload (17). Gradient echo (GRE) sequences can be made predominantly T2* weighted by using a low flip angle, long echo time, and long repetition time. GRE sequences with T2*-based contrast are used to depict hemorrhage, calcification, and iron deposition in various tissues and lesions (18).

One of the most complications of thalassemia is the cardiovascular type. The cardiovascular complications cause 71% mortality rate in BT patients (1,13). Iron overload is caused changes in arterial structure and atherosclerotic plaque formation in BT major patients (19-21). Iron, as a catalytic agent, accelerates the low-density lipoprotein (LDL) oxidation. Oxidized LDL is recognized by macrophages; accordingly, accumulation of lipid in these cells and formation of foam cells is occurred. Foam cells are characteristic cells in early onset atherosclerosis. Oxidized LDL also causes changes in endothelial cell integrity by its cytotoxic effect and diapedesis of circulating monocyte by its chemotactic effect. Therefore, the atherosclerotic lesions are progressed (1, 3, 5, 9, 19, 20, and 22). Color Doppler ultrasound of carotid artery is a non-invasive and available method for early detection of atherosclerosis in BT patients.

Increased carotid intima media thickness (CIMT) is a useful marker for atherosclerosis (5,20). The test measures the thickness of the inner two layers of the carotid artery-the intima and media- and alerts physicians to any thickening when patients are still asymptomatic (23).

In the present study, we aim to measure CIMT in BT major patients as a marker for early detection of atherosclerosis and compare the results with healthy control group. Then, we assess the relationship between iron overload level and the occurrence of BT major which is evaluated by cardiac and hepatic MRI T2*. In addition, the effect of different factors, such as age, sex, age at diagnosis, age at the beginning of transfusion, chelation therapy type, and duration on CIMT in these patients is investigated. Early detection of atherosclerosis and early chelation therapy is resulted in decreasing the adverse effect of iron overload in BT major.

Materials and Methods

This study was a cross-sectional study with two case/control groups that was performed in 2018 on twenty patients with BT major and twenty normal healthy sex- and age-matched group, as control. Patients of the control group were from the Ghaem and Emdad hospitals (Mashhad, Iran). The case group was referred to the Sarvar thalassemia clinic (Mashhad, Iran) for their periodic blood transfusion and had previous documents there. The demographic data was extracted from their documents; for example, age, sex, weight, chelation therapy type, age at the beginning of chelation therapy, age at the beginning of blood transfusion, transfusion volume and interval, and age at diagnosis. All patients were received regular transfusion and chelating therapy from their childhood. Patients with history of smoking, cardiac

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abnormality, atrial fibrillation, arterial hypertension, hyperlipidemia, diabetes mellitus, thyroid dysfunction, and those who received cardiac drugs were excluded from the study. The selected patients were those who performed hepatic and cardiac MRI T2* recently in 2016, 2017, and 2018. Iron overload was detected with quantitative T2*. CIMT was measured with high frequency probe in right and left side. The control group was selected from healthy population referred to the clinic for other causes unrelated to thalassemia patients and were matched with case group on the base of age and sex.

Color Doppler ultrasound

In all BT major patients and control group, B-mode and color-coded duplex ultrasound were performed with Esoate Mylab ™ Six machine (Esoate, Italy) and by 3-13 MHZ large broad band high frequency vascular linear array SL1543 transducer. Common carotid, internal carotid, and external carotid artery were assessed in both sides. The study was started with placing the probe on common carotid arteries (CCA) in lower cervical area in transverse plane. We angulated the transducer to caudal for evaluating the CCA origin from brachiocephalic artery in the right and aortic arch in the left. Then, CCA was followed to cranial direction until CCA bifurcation was appeared and its two branches, internal carotid arteries (ICA) and external carotid arteries (ECA), were traced until the probe was blocked by mandible bone. This examination was repeated in longitudinal plane parallel to long axis of CCA. These vessels were evaluated for the presence of atherosclerotic plaque, other obstructive lesions, and sub-intimal lucencies that bulged into arterial lumen. At the end, intima media thickness (IMT) was measured in longitudinal plane in 2 cm proximal to CCA bifurcation, ICA, and ECA. For IMT measurement, the cursor was placed in the junction of lumen and intima and continued to the junction of media and adventitia (from the first echogenic line to the second echogenic line) in far arterial wall. These measurements were done in each of common carotid artery, internal carotid, and external carotid for three times. Then, the average was determined.

Hepatic MRI T2*

Iron overload in liver was estimated by using MRI as a non-invasive method. MRI was performed with 1.5 Tesla Siemens Avanto machine (Siemens, Germany). A standard quadrature radio frequency (RF) body coil was used in all measurements for signal detection and stimulation. All individuals were positioned in supine and entered magnet cradle. Respiratory triggering head-first configuration was used for breath monitoring and spatial pre-saturation slab for motion related artifact suppression. MRI T2* was provided successfully from 12 axial images of liver from hepatic center next to large vessels (hepatic hilum) with 12 different TEs (TE= echo time, from 1.29 ms to 22.14 ms). Each of images was obtained in gradient echo sequence with 25s breathe hold using the setting of: repetition time (RT)=200 ms, flip angel=20 degrees, matrix resolution=128 pixels, field of view (FOV)=96 ×128, sampling bandwidth=1950 hz/px, slice thickness=10 mm, and FOV phase=75%. Then, signal intensity of liver parenchyma was measured in three region of interest (ROI) (greater than 1 cm^2); one ROI in the right, and two ROIs in the left liver lobe. One ROI was measured in each paraspinal muscle for comparison. The mean signal intensity of liver to muscle was calculated for each sequence. Final value of hepatic intracellular iron concentration was measured with special software. Patients were divided into four groups based on their hepatic iron overload severity from MRI T2* results: greater than 6.3 ms (normal), 2.8-6.3 ms (mild), 1.4-2.7 ms (moderate), lower than 1.4 ms (sever).

Cardiac MRI T2*

Cardiac MRI T2* was obtained by 32-channel phase array coil using 14s breath hold bright blood Multi-echo GE sequence.

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Eight short axis images at the level of papillary muscle in mid-ventricular area with eight different TEs (from 2.97 ms to 21.63 ms) were provided. Other settings were: RT=200 ms, slice thickness=10mm, flip angel 20 degrees, FOV=256×77, sampling bandwidth=810 hz/px, matrix resolution=256 ms, and FOV phase=75%. Three or four ROIs were drawn manually which contained entire intra-ventricular septum thickness except blood pool far from cardiac apex and confined with superior and inferior intra-ventricular insertion points. The mean signal intensity of ROIs was calculated for each of eight images. Then, a curve was drawn at the end. Patients were divided into four groups based on their cardiac iron overload severity from MRI T2* results: greater than 20 ms (normal), 14-20 ms (mild), 10-14 ms (moderate), lower than 10 ms (sever).

The cardiac iron overload was divided into two groups: normal and abnormal. Hepatic iron overload was also divided into two groups: normal and mild, moderate and more. Then, mean CIMT was measured in these groups. The type of chelators was divided into two groups: Desferal and non-Desferal.

Ethical consideration

This study was approved by ethical committee of Mashhad University of Medical Sciences (IR.MUMS.FM.REC.1396. 697).

Statistical analysis

Quantitative variables were explained in the form of mean ± standard deviation (S.D.), but qualitative values were reported in the form of numbers and percentile. Independent student t-test was used for the comparison of quantitative variables with normal distribution, but Mann-Whitney U test for the abnormal distribution ones between two groups. Qualitative variables were compared by Chi-square. Pearson correlation coefficient was used for variables with normal distribution, but Spearman correlation coefficient was used for the abnormal ones. P-values lower than 0.05 were statistically significant in all evaluations. All data were analyzed using SPSS software.

Results

Among BT major patients, seven females (35%) and thirteen males (65%) were attended in our study. In the control group, eleven females (55%) and nine males (45%) were considered. The average age of BT patients was 21.3 ± 8.2 years and similar age distribution was in the control group (22.8 ± 11.0 years). Other basic information is summarized in Table I.

Type of chelators was different among our patients. Most of our patients were advised Deferoxamine (Desferal) (35%) and Desferal+Deferiprone (L1) (Table II). The patients had most frequently no cardiac involvement (65%) and the second most common cardiac iron overload was moderate (Table II). Mild hepatic involvement was detected in most of our BT patients (Table II).

The average IMT of right and left common carotid, internal carotid, and external carotid arteries was insignificantly higher in the case group than the control group and only right common carotid arteries (RCCA) and right internal carotid arteries (RICA) had significant difference between two groups (Table III). No correlation was found between hepatic and cardiac iron overload based on MRI T2* results and CIMT. However, mild correlation was detected in left internal carotid arteries (LICA) (Table IV).

The same results were obtained when comparing IMT with hepatic and cardiac involvement severity, which were not significant in any of mentioned groups (Table V). There was no correlation between age and sex with CIMT measurements. Moderate correlation was found between RICA-CIMT and age at diagnosis and between age at the beginning of transfusion and CIMT, but generally there were no correlations between other CIMT measurements and age at diagnosis and age at the beginning of transfusion. Also, age at the beginning of chelator drugs

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had no relationship with CIMT among beta thalassemia patients (Table VI).

In our study, no relationship was found between CIMT measurements and chelation type (ANOVA results, Table VII). There was a borderline relationship between chelator type and cardiac overload, but there was no relationship between chelator type and hepatic iron overload (Table VIII).

Table I: Basic information of the beta thalassemia patients participated in the present study

Characteristics	Minimum	Maximum	Mean ± S.D.
Weight (Kg)	29	68	49.6 ± 11.5
Age at diagnosis (Month)	3	108	20.4 ± 31.5
Age at the beginning of transfusion (Month)	3	108	22.6 ± 32.7
Transfusion volume (IU)	1	3	2.05 ± 0.30
Transfusion interval (Days)	20	25	21.7 ± 1.70
Age at the beginning of chelation (Year)	1	15	4.72 ± 4.45

S.D.=Standard deviation; IU=International unit

Table II: Chelator type, cardiac involvement severity, and hepatic involvement severity in the participated patients in the present study

		Number of patients	Percentage
Chelator type	Desferal	7	35%
	Desferal+L1	7	35%
	Exjade	2	10%
	Osveral	4	20%
Cardiac involvement severity	Normal	13	65%
	Mild	1	5%
	Moderate	4	20%
	Sever	1	5%
	Very sever	1	5%
Hepatic involvement severity	Normal	2	10%
	Mild	9	45%
	Moderate	4	20%
	Sever	3	15%
	Very sever	2	10%

Exjade=Deferasirox; L1=Deferiprone; Desferal=Deferoxamine

Table III: The average intima media thickness (IMT) of right and left common carotid, internal and external carotid arteries in the patients

	Case group	Control group	P-value
Right common carotid	0.49 ± 0.05	0.45 ± 0.03	**0.009**
Right internal carotid	0.45 ± 0.07	0.40 ± 0.08	**0.049**
Right external carotid	0.39 ± 0.08	0.36 ± 0.05	0.20
Left common carotid	0.48 ± 0.06	0.46 ± 0.04	0.17
Left internal carotid	0.44 ± 0.07	0.40 ± 0.06	0.05
Left external carotid	0.37 ± 0.05	0.34 ± 0.05	0.60

The values are mean ± standard deviation (S.D.). P-values show the comparison between case and control group for each measurement using t-test. The significant P-values are shown in bold ($p < 0.05$).

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Table IV: The correlation between hepatic and cardiac iron overload based on MRI T2 results and carotid intima media thickness (CIMT)*

		Cardiac involvement severity	Hepatic involvement severity
Right common carotid artery	Correlation	0.13	0.08
	P-value	0.57	0.72
Right internal carotid artery	Correlation	0.06	0.14
	P-value	0.80	0.53
Right external carotid artery	Correlation	0.049	0.20
	P-value	0.83	0.38
Left common carotid artery	Correlation	0.01	0.08
	P-value	0.94	0.71
Left internal carotid artery	Correlation	0.42	0.38
	P-value	0.06	0.09
Left external carotid artery	Correlation	0.07	0.24
	P-value	0.78	0.29

Table V: The average of intima media thickness (IMT) in different cardiac and hepatic iron overload groups of patients

	Cardiac iron overload	Mean IMT	P-value	Hepatic iron overload	Mean IMT	P-value
Right common carotid	Normal	0.49 ± 0.05	0.72	Normal+mild	0.48 ± 0.05	0.51
Right common carotid	Abnormal	0.48 ± 0.05		Moderate+more	0.50 ± 0.05	
Right internal carotid	Normal	0.46 ± 0.07	0.79	Normal+mild	0.45 ± 0.07	0.97
Right internal carotid	Abnormal	0.45 ± 0.07		Moderate+more	0.45 ± 0.06	
Right external carotid	Normal	0.39 ± 0.09	0.96	Normal+mild	0.40 ± 0.09	0.44
Right external carotid	Abnormal	0.39 ± 0.07		Moderate+more	0.37 ± 0.08	
Left common carotid	Normal	0.49 ± 0.07	0.81	Normal+mild	0.47 ± 0.05	0.33
Left common carotid	Abnormal	0.48 ± 0.06		Moderate+more	0.50 ± 0.08	
Left internal carotid	Normal	0.46 ± 0.06	0.36	Normal+mild	0.46 ± 0.07	0.33
Left internal carotid	Abnormal	0.42 ± 0.09		Moderate+more	0.43 ± 0.08	
Left external carotid	Normal	0.36 ± 0.05	0.90	Normal+mild	0.37 ± 0.05	0.63
Left external carotid	Abnormal	0.37 ± 0.07		Moderate+more	0.36 ± 0.06	

The presented values are mean ± standard error (S.D.). The P-values are the results of comparing different groups.

Table VI: The effect of age at the beginning of chelator drugs with carotid intima media thickness (CIMT) among beta thalassemia patients

		Age	Age at diagnosis	Age at the beginning of transfusion	Age at the beginning of chelation
Right common carotid artery (RCCA)	Correlation	0.39	0.16	0.16	-0.08
	P-value	0.09	0.49	0.49	0.74
Right internal carotid artery (RICA)	Correlation	0.42	0.53	0.50	0.04
	P-value	0.07	0.02	0.02	0.86
Right external carotid artery (RECA)	Correlation	0.11	0.09	0.10	0.09
	P-value	0.64	0.70	0.69	0.71
Left common carotid artery (LCCA)	Correlation	0.76	0.34	0.30	0.07
	P-value	0.00	0.14	0.20	0.78
Left internal carotid artery (LICA)	Correlation	0.42	0.37	0.33	0.19
	P-value	0.06	0.10	0.16	0.43
Left external carotid artery (LECA)	Correlation	0.03	0.12	0.16	0.15
	P-value	0.89	0.60	0.51	0.52

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Table VII: The relationship between carotid intima media thickness (CIMT) measurements and chelation type based on ANOVA

	Chelator type	Mean	P-value
RCCA	Desferal	0.50 ± 0.03	0.51
	Desferal+L1	0.51 ± 0.05	
	Exjade	0.50 ± 0.00	
	Osveral	0.50 ± 0.08	
RICA	Desferal	0.44 ± 0.09	0.96
	Desferal+L1	0.46 ± 0.07	
	Exjade	0.44 ± 0.00	
	Osveral	0.46 ± 0.05	
RECA	Desferal	0.39 ± 0.09	0.84
	Desferal+L1	0.37 ± 0.08	
	Exjade	0.39 ± 0.00	
	Osveral	0.42 ± 0.10	
LCCA	Desferal	0.49 ± 0.08	0.91
	Desferal+L1	0.50 ± 0.07	
	Exjade	0.47 ± 0.01	
	Osveral	0.47 ± 0.06	
LICA	Desferal	0.43 ± 0.08	0.91
	Desferal+L1	0.46 ± 0.08	
	Exjade	0.45 ± 0.04	
	Osveral	0.46 ± 0.07	
LECA	Desferal	0.35 ± 0.04	0.63
	Desferal+L1	0.37 ± 0.07	
	Exjade	0.37 ± 0.03	
	Osveral	0.40 ± 0.06	

The values are mean ± standard deviation (S.D.). See Table VI for abbreviations. Exjade=Deferasirox; L1=Deferiprone; Desferal=Deferoxamine

Table VIII: The relationship between chelator type and cardiac/hepatic overload in the participated patients

Chaletor type	Cardiac iron overload		Total	P-value	Hepatic iron overload		Total	P-value
Desferal	Normal	Abnormal		0.05	Normal	Abnormal		0.16
	7	7	14		6	8	14	
	50%	50%	100%		42.9%	57.1%	100%	
Non-Desferal	6	0	6		5	1	6	
	100%	100%	100%		83.3%	16.7%	100%	

Discussion

Our study demonstrated insignificantly higher mean CIMT measurements of external, internal, and common carotid in both sides in BT major patients compared to healthy control group. These differences were only significant for the right common and internal carotid (0.49 ± 0.05 vs. 0.45 ± 0.03 and 0.45 ± 0.07 vs. 0.40 ± 0.08, Table V). This finding is in agreement with most previous studies that showed significant increase of CIMT in BT patients compared to the control group (1,3-5,13,20-22,24-27). The reasons of insignificant increase in CIMT in BT major patients in the comparison with age- and sex-matched control group in most of our measurements may be: 1) the mean age of the patients attended in our study was low (21.3 ± 8.20 years), so this age was too early for initiation of the atherogenic effect of iron and development of CIMT; 2) the low mean

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age of our patients at diagnosis (20.4 ± 31.5 months) and starting chelation therapy (4.72 ± 4.45 years) showed that early detection and treatment prevented adverse effects of transfusion and iron overload and caused reduction of IMT among them; 3) most patients in our study had normal to mild hepatic and cardiac involvements on the basis of MRI T2*, so the total body iron did not reach to the high level which is essential for atherosclerosis development. It should be noted that atherosclerosis development can be detected by an increase in CIMT.

Few studies showed opposite results in which the CIMT was similar in case and control groups, but arterial stiffness was increased significantly among thalassemia patients (2,9). Similar to our study (with significant difference in CIMT between case and control group), Abaza et al. (20) clarified the significant increase in mean CIMT solely in right anterior, right posterior, and left anterior arterial wall in BT major group compared to control. This increase was regardless of iron overload. This means that CIMT level is not influenced by iron deposition amounts. Also, there were no differences in CIMT between men and women and those with good or poor compliance to chelation drugs in the present study. In contrast to our study, Kraml et al. (19) demonstrated strong relationship between asymptomatic carotid atherosclerosis and iron deposition in both men and women in beta thalassemia major. But, IMT had positive relationships with transfusion duration and duration of disease occurrence.

Our study represented no relationship between CIMT and patients' age and sex, chelator type, and hepatic and cardiac iron overload in BT major. Only moderate correlation was found between right internal carotid IMT and age at diagnosis, and age at the beginning of transfusion. Other CIMT measurements did not correlate with age at the diagnosis of BT major, age at the beginning of transfusion, and age at the beginning of chelation therapy. Several studies reported significant increase of IMT in men and with rising age. These results are in contrast with ours (5,22,25). Abdelsamei et al. (5) showed positive relationship between the duration of first transfusion and CIMT. Therefore, the longer time passed from the first transfusion, the higher level of IMT should be expected and more atherogenic effects should be detected. Akhlaghpour et al. (3) reported no correlation between mean IMT and hepatic iron overload in 10-19 years old group in BT major patients; but in other age groups, an increase of IMT was found with increasing hepatic iron overload severity.

In our study, half of the fourteen BT major patients who received Desferal (50%) and none of the six patients who received non-Desferal drugs, had cardiac iron overload (Table VIII). Although, there was only a borderline relationship between cardiac iron deposition severity and chelator type, but this significant difference was demonstrated lower efficacy of Desferal on myocardial iron overload. So, the patients with Desferal consumption were suffered from cardiac involvement. In Desferal group, eight out of fourteen (57.1%) and in non-Desferal group, one out of six (16%) had moderate or more hepatic iron overload severity (Table VIII). Although, there was no significant relationship between hepatic iron overload and chelator type, this difference may be implicated to the lower effectiveness of Desferal on hepatocyte iron deposition. Thus, the importance of non-Desferal drugs on hepatic and myocardial iron overload may be characterized. These statistically insignificant findings may be due to small sample size in our study; therefore, further studies would be necessary to obtain more precise comparisons.

Wahidiyat et al. (7) showed DFP preference for myocardial and DFO for hepatic iron overload. Ansari et al. (17) represented the significant influence of combined or monotherapy of DFX in decreasing myocardial and hepatic overload and

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improving MRI T2* values. No significant improvement was found in serum ferritin and MRI T2* (hepatic and cardiac) using DFO after twelve months. DFP alone or combined with DFO demonstrated a selective choice for myocardial iron overload in previous research (6,13). This result may be due to better compliance of DFP and DFX with one-dose oral daily use in comparison with DFO in the form of subcutaneous injection. A clue challenge of chelation therapy is regular consumption of drugs; so that even a short course of treatment cessation would be resulted in hazardous influence on body organs (10,28). However, a recent study showed no difference in the presence or absence of compliance (20).

The limitations of our study were small sample size and difficulty in finding thalassemia patients without cardiac disease. Most of the BT major patients were used cardiac affecting drugs and suffered from some degrees of cardiac insufficiency. Generally, our studied population was young children and adolescence; therefore, limited exposure time of thalassemia and iron overload would be expected that could have influenced our results.

Our findings suggest that early detection of vascular problems, such as atherosclerosis, can be found with Doppler ultrasound prior to the measurement of T2* values (due to iron overload) in beta thalassemia patients. Further research should be done with greater sample size on better indices other than CIMT that can detect atherosclerotic plaque formation and progression. In addition, better chelation agents should be assessed for the reduction of hepatic and cardiac MRI T2* values. MRI T2* is an expensive method, not available everywhere, and not easily applicable for children. Moreover, an experienced radiologist is needed for interpretation of the results. Therefore, other alternative methods for detecting iron overload must be planned.

Conclusion

Preventive and curative methods should be planned to cease atherosclerosis progression. Furthermore, early initiation of chelator drugs with better efficacy and compliance may reverse the hepatotoxic and adverse myocardial effects of excessive iron.

Conflict of interest

The authors declare no conflict of interest.

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