Influence of Average Annual Mean Serum Ferritin Levels on Left Ventricular Function in Patients With β Thalassemia

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Received: 08 Jan. 2020; Accepted: 18 May 2020

Abstract- Cardiac complications are the most important cause of mortality and morbidity in Beta-Thalassemia Major (B-TM). The aim of our study was to determine the influence of Average Annual Mean Serum Ferritin (AAMSF) levels on cardiac function in patients suffering from B-TM. In this cross-sectional study, 50 patients of 5-15 years with B-TM were enrolled in the absence of clinical signs and symptoms of cardiac dysfunction. Left ventricular function was studied by using tissue Doppler image (TDI), pulse wave Doppler (PWD). AAMSF level was measured for 12 months. Patient groups were subdivided into two groups, group A with AAMSF level below 1000 ng/ml and group with B with AAMSF level above 1000 ng/ml. The Case group included 24(48%) males and 26(52%) females which were compared with 50 healthy subjects composed of 27(54%) males and 23 (46%) females (control group). The AAMSF Levels were 1054.60±687.95 ng/ml. By using PDW, in patients with AAMSF below 1000 ng/ml, The Parameters of the E, A, E/A E-DT had no significant difference with health groups (*P*=0.808, *P*=0.820, *P*=0.231 and *P*=0.061, respectively). No significant difference was revealed in parameters of E', IVCT and ET in patients with AAMSF below 1000 ng/ml by using TDI in comparison to control (*P*=0.155, *P*=0.683, *P*=0.222, respectively).however, other TDI indexes including A', E'/A', IVRT, S,' LVMPI, E/E' had a significant difference with health group (*P*=0.014, *P*=0.041, *P*=0.045, *P*=0.002, *P*=0.021, and *P*=0.002, respectively). At patients with above AAMSF 1000 ng/mL, both PDW and TDI parameters had significant differences with the health group. There was no correlation among AAMSF levels and PWD or TDI indexes. The evidence from this study suggests that subclinical systolic and diastolic LV dysfunction has happened with AAMSF level above 1000 ng/ml, and according to our result, TDI is found more useful than PWD for subclinical cardiac evaluation.

Acta Med Iran 2020;58(6):279-284.

Keywords: Beta-thalassemia major; Children; Cardiac function; Pulse wave doppler; Serum ferritin; Tissue doppler image

Introduction

Thalassemia is the most common genetic disorder in the entire world (1). Frequent blood transfusion is a mainstay of treatment in major thalassemia, which is often linked to iron overload. Iron accumulates IN various organs, especially the heart, hence leading to HF heart failure, the primes cause of death in patent suffering from B-TM. Several methods are applied to measure iron levels. The measurement of serum ferritin is a relatively reliable test (2). Serum ferritin levels are commonly used to assess the severity of iron overload. In clinical practice, serum ferritin has been measured to assess the effectiveness of treatment. We used the AAMSF level as iron overload in pediatric patients with major thalassemia. AAMSF can be useful because it is a marker of long term iron status. The TDI and PWD echocardiography have been recently used to evaluate early myocardial dysfunction in patients with thalassemia (3). The aim of this study was to determine the correlation

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between PWD and TDI echocardiographic indexes and the AAMSF level.

Materials and Methods

This study was designed as a cross-sectional study on pediatric asymptomatic beta-thalassemia patients, which was performed from April 2016 to April 2017. The study protocol was approved by the local Research Ethics Committee of our center. In this study, 50 thalassemia patients (23females, 27 males) aged with range 5-15 years were compared with 50 age and gender-matched controls.

All patients received regular blood transfusions at 3-4 week intervals in order to maintain hemoglobin level above 10 g/dl. Iron chelation therapy was performed according to hematology guidelines, either as deferiprone (DFP), deferoxamine (DFO), or both. During one year follow-up, the patients with cardiac arrhythmia, hypertension, left ventricular ejection fraction (LVEF) less than 55% were excluded. All subjects were evaluated for past medical history, physical examination, echocardiography, measurements, and laboratory tests (hemoglobin and serum ferritin). Average Annual Mean Serum Ferritin (AAMSF) levels were calculated from previous levels of serum ferritin during the one year follow up. In our study, the severity of iron overload was determined by AAMSF levels. Therefore, group A patients with levels below 1000 ng/ml were considered suitable candidates for iron chelator therapy, in spite of group B patients with the level above 1000 ng/ml.

Echocardiography

Echocardiographic assessments were performed using a 3-8 MHz probe by ViVid 6 (GE Medical Systems, general electric, USA). Echocardiography was performed from the parasternal long-axis and the apical four chambers view. Before cardiovascular assessments, all participants were given a 30-minute rest.

In both groups, ventricular functions were evaluated by M-mode, TDI, and pulsed-wave Doppler. We applied echocardiographic parameters in 5 consecutive cardiac cycles to confirm the analysis, and the echocardiography technique was performed according to American society echocardiography.

Standard echocardiography

In the Standard Echocardiography, we measured fractional shortening, Ejection Fraction(EF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and the left atrial and aortic diameters (LA/AO) ratio, Interventricular septal dimension in systole, left ventricular end-diastolic volumes(LVEDV), Posterior wall thickness (PWT) and Septal wall thickness (SWT) were determined in the apical four-chamber view.

Pulse wave doppler echocardiography

In the case group, the cardiac evaluation was performed before blood transfusion. Diastolic function was evaluated by the PWD of the mitral valve. The PWD was assessed by placing the sample volume 3-5 mm above the tip of the mitral valve. The Peak mitral inflow velocity at early diastole (E), atrial contraction (A), E/A ratio, and E wave deceleration time (E-DT) were measured. Diastolic dysfunction was defined as the presence of any abnormalities in one of the mentioned parameters.

Tissue doppler imaging echocardiography

The TDI parameters were assessed by placing the sample volume at the basal RV free wall segment for tricuspid and the lateral LV wall for mitral annulus. At the lateral LV wall and at the basal RV segment, by systolic myocardial velocity (S’) we evaluated systolic parameters, and early (E’) and late (A’) diastolic velocities, (E’/A’ ratio) and isovolumetric relaxation time (IVRT) were determined as diastolic parameters. The Myocardial performance index MPI (IVRT+IVCT/ET) was calculated to assess systolic and diastolic function simultaneously. The E/E’ Raito was calculated as an index of LV filling pressure. At the basal RV free wall segment, the systolic and diastolic right ventricular function was measured as S’, E,’ A,’ E’/A’ ratio, IVRT, and MPI parameters.

Measurement of serum ferritin levels

The serum ferritin level was measured with technical ELISA (Awareness technology, US). The serum ferritin levels were measured before blood transfusion. Afterward, the mean serum ferritin level was recorded for 12 months. Measurement was conducted on lacked evidence of infection.

Statistical analysis

All variables were expressed as mean±standard deviation, and data analysis was performed using the software version SPSS 20 (SPSS, Inc., Chicago, IL, USA). Statistical analysis was performed using Independent samples Student *t*-test and *chi*-square test. Pearson correlation coefficient analyses were employed to assess the relationship between echocardiographic parameters and AAMSF levels. A P of <0.05 was considered to be statistically significant.

Results

In our study, 50 B-TM patients 24(48%) males and 26(52%) females were compared with 50 healthy subjects, 27(54%) males and 23(46%) females (control group). Table 1 summarizes the demographic characteristics of the study population. The analysis did not reveal any significant difference with regard to body mass index (BMI), heart rate (HR), systolic, and diastolic blood pressure (SBP-DBP) between two groups. The AAMSF Levels were 1054.60±687.95 ng /ml.

Table 1. Demographic and clinical characteristics of b thalassemia patients according to the serum level of ferritin

	Total (B-TM) (n=50)	Control (n=50)	*P*
Gender (F/M) (%)	26/24 (%52-%48)	23/27	
Age (year)	23.80±7.84	23.69±5.89	*P*=0.937
BMI(Kg/M²)	20.54±3.43	21.69±1.72	*P*=0.037
HR (Bpm)	72.39±7.41	73.79±6.71	*P*=0.325
SBP(mmHg)	116.33±6.02	114.69±4.62	*P*=0.130
DBP(mmHg)	76.65±5.14	77.95±4.74	*P*=0.192
Hemoglobin	9.39±0.91	14.75±2.29	*P*=0.0001
Ferritin (ng/mL)	1054.60±687.95	110 .93±55.97	*P*=0.0001
Splenectomy	4	-	-
Age of chelator therapy (yr)	10.34±7.98	-	-
Age of Blood transfusion (yr)	12.57±8.54	-	-
Total transfusion (times/year)	12.10±0.89	-	-

BMI: Body Mass Index, HR: Heart Rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure

Tables 2 and 3 summarizes PWD, TDI, and standard echocardiographic. There was no significant difference by using standard echocardiography between two groups.

In patients with AAMSF level above 1000 ng/mL, subclinical left ventricular diastolic dysfunction was identified by using PWD and TDI. However, in patients with AAMSF below 1000 ng/mL, no significant difference was revealed in left ventricular diastolic function between two groups as determined by PWD echocardiography.

Table 2. Comparison of the standard echocardiography data in serum ferritin groups

	Case (n=50)	Control (n=50)	*P*
EF (%)	67.85±2.63	68.97 ± 3.55	*P*=0.076
FS (%)	33.45±2.16	33.48±3.68	*P*=0.961
IVSD(mm)	3.73 ± 1.59	3.56 ±1.90	*P*=0.629
LVPWD(mm)	3.12 ± 1.59	3.10 ± 1.46	*P*=0.948
IVSS(mm)	5.43 ± 1.48	5.35 ± 1.94	*P*=0.817
LVPWS(mm)	5.33±1.88	5.13±1.48	*P*=0.556
LVEDD(mm)	49.31±6.43	48.31±5.98	*P*=0.423
LVESD(mm)	34.87±7.89	32.93±7.67	*P*=0.216
AO/LA(ratio)	1.29±0.27	1.22±0.17	*P*=0.124

IVSD: Interventricular septal dimension in diastole; LVPWD: Left ventricular posterior wall dimension in diastole; IVSS: Interventricular septal dimension in systole; LVPWS: Left ventricular posterior wall dimension in systole; LVEDD: Left ventricular end-diastolic dimension; LVESD: Left ventricular end-systolic dimension; EF: Ejection fraction; SF: Shortening fraction; AO: Aorta Diameter; LA: Left atrium diameter; AO/LA: Aorta/Left atrium diameter

There was no significant difference between patients with AAMSF below 1000 ng/mL and health groups in The IVCT parameter. No significant difference was identified between three groups in the ET parameter. The E' parameter had no significant difference by using TDI between patients with AAMSF below1000 ng/mL and health group, but other TDI variables including A', E'/A', IVRT, S,' LVMPI, E/E' had significant difference with health group.

The LVMPI and E/E' were increased in all patients relative to health groups (*P*=0.021 and *P*=0.002, respectively). There was no correlation among AAMSF levels and PWD, TDI, or standard echocardiography. No correlation was found between echocardiographic parameters and AAMSF levels in both patients with AAMSF level above and below 1000 ng/ml.

Table 3. Comparison of the PWD and TDI in serum ferritin groups

	Total case (n=50)	<1000 ng/mL (n=32)	>1000 ng/ml (n=18)	Control (n=50)
E(m/sec)	102.20±8.01 (*P*=0.487)	102.82±8.24 (*P*=0.808)	101.10±7.68 (*P*=0.264)	103.22 ± 6.53
A(m/sec)	54.87±5.82 (*P*=0.080)	55.16±6.14 (*P*=0.082)	54.36±5.32 (*P*=0.323)	52.88 ± 5.42
E/A(ratio)	1.88±0.23 (*P*=0.0001)	1.69±0.26 (*P*=0.231)	1.87±0.17 (*P*=0.0001)	1.63 ± 0.19
E-DT(msec)	135.86±22.70 (*P*=0.001)	140.93±22.83 (*P*=0.061)	123.22±24.93 (*P*=0.0001)	149.76 ± 18.95
E'(msec)	18.21±2.60 (*P*=0.004)	18.99±2.77 (*P*=0.155)	17.61±2.28 (*P*=0.007)	20.02 ± 3.40
A'(msec)	6.38±1.08 (*P*=0.036)	6.99±1.89 (*P*=0.014)	6.81±1.07 (*P*=0.015)	7.89 ± 1.35
E'/A'(ratio)	3.81±0.44 (*P*=0.004)	3.03±0.25 (*P*=0.041)	3.97±0.89 (*P*=0.021)	3.38 ± 0.93
IVRT(msec)	96.49±11.28 (*P*=0.008)	95.55±10.98 (*P*=0.045)	98.15±11.96 (*P*=0.021)	90.04 ± 12.53
S'(msec)	8.49 ± 1.20 (*P*=0.036)	8.02 ± 1.16 (*P*=0.002)	7.53 ± 1.39 (*P*=0.0005)	9.09 ± 1.60
LVMPI	0.41±0.09 (*P*=0.021)	0.40±0.02 (*P*=0.041)	0.42±0.08 (*P*=0.026)	0.37±0.08
E/E'(ratio)	5.73±0.95 (*P*=0.002)	5.55±0.39 (*P*=0.007)	5.91±1.07 (*P*=0.001)	5.24±0.55
IVCT(msec)	33.78±13.62 (*P*=0. 234)	31.62±11.74 (*P*=0.683)	38.99±10.66 (*P*=0.031)	30.33±15.12
ET(msec)	251.24±43.36 (*P*=0.178)	252.33±38.24 (*P*=0.222)	251.25±41.36 (*P*=0.241)	260.67±23.17

MPI: Myocardial performance index; LVMI: Left ventricular mass index; PEP: Pre-ejection period; ET: Ejection time; PEP/ET: Pre-ejection period/Ejection time; ICT: Isovolumic contraction
n time; IRT: Isovolumic relaxation time; AT: Acceleration time; DS: Deceleration slope; DT: Deceleration time; Peak E: Peak E velocity; Peak A: Peak A velocity; E/A: E/A velocity ratio

Discussion

Iron deposition in cardiac tissue is an important complication of B-TM, which leads to tissue degeneration and fibrosis, hence ventricular dysfunction. The measurement of serum ferritin is an indirect marker of cardiac involvement, which is of no value in inflammatory conditions (4). In recent years, many methods have been taken into account for exact cardiac evaluation. Standard Echocardiography is useful to study anatomical changes of the heart. The PWD and TDI are two methods for exact subclinical systolic and diastolic dysfunction in patients.

In the present study, AAMSF Level was measured in 50 patients with β-thalassemia. The AAMSF Levels were 1054.60±687.95 ng/dl. In this study, subclinical cardiac systolic and diastolic dysfunction was evaluated in B-TM patients 5-15 years. By using M-Mode echocardiography, cardiac function was preserved, and LV diameters in systolic and diastolic phases had no significant difference with the control groups.

Oscal B *et al*., showed that the mean IVSD of patients group was higher than the control group, which in contrast with our findings (5). We also did not find a significant association between AAMSF Levels and standard echocardiography parameters.

Eghbali *et al*., found a weak positive correlation between ferritin level and M-mode echocardiography parameters (6). Kyriacou K *et al*., demonstrated that patients with higher ferritin levels presented with higher LVDdT and lower EF and FS (7). In contrast to a study conducted by P. Roeser *et al*., no correlation was identified between levels of the LVEF (8).

Shahmohammadi P *et al*., also showed no significant correlation between echocardiography findings and ferritin levels, which were both consistent with our findings (9). Another study reported that patients with less than ferritin level 2500 ng/ml had normal systolic and diastolic function (10).

In our study, cases were subdivided into two groups with AAMSF levels below, and above 1000 ng/ml had no significant difference with regard to M- Mode parameters and LV geometry, however significantly differed from the controls.

According to our study, it was found that subclinical systolic and diastolic damage ever in patients with AAMSF level less than 1000 ng/ml. No correlation was found among DTI or PWD parameters and the AAMSF level. To put differently, systolic and diastolic LV dysfunction were found similar in all patients with serum ferritin level above and below 1000 ng/ml.

Diastolic dysfunction was absent in all patients with AAMSF less than 1000 ng/mL, based on PWD, and was present in all patients with AAMSF above 1000 ng/mL based on TDI.

Our results also differ considerably from those of K, Papadopoulou-Legbelo *et al.,* who noted that ferritin was associated with echocardiography findings such as early & late peak of flow velocity (E/A), EF and FS (11).

Decreased E-DT and increased early ventricular filling velocity/early diastolic myocardial velocity (E/E' Ratio) indicated diastolic LV dysfunction according to high left ventricular end-diastolic pressure (LVEDP) and increased left atrial pressure. In our study, all of the patients with AAMSF levels above 1000 ng/ml had abnormal E-DT and E/E' Ratio measurements.

Modell *et al*., demonstrated that a decrease in Declaration Time (DT), an increase in E/Em ratio, and Mitral A wave peak flow, in other words, subclinical diastolic dysfunction happened in patients (10).

Assessment of diastolic LV function in pediatric patients should be not only be interpreted by the PWD flow pattern. Therefore, TDI may permit early detection of cardiac ventricular dysfunction.

In our study, the S' index was below the normal range of healthy subjects in both groups of cases with serum ferritin levels below, and above 1000 ng/ml, therefore systolic dysfunction was observed even in patients with AAMSF levels below 1000 ng/ml.

Increased MPI reflects both systolic and diastolic ventricular dysfunction. In our study, LVMPI was significantly increased in comparison to the control group. IVRT and IVCT were also significantly increased along with a decrease in ET (12).

Ventricular relaxation in diastolic was evaluated by measuring IVRT. The IVRI was increased in our study. Therefore, subclinical diastolic dysfunction had already occurred even patients younger than 15-year-old this was also compatible with the finding of other studies (13,14).

In our study, we found that Annual Mean Serum Ferritin Levels had no correlation with TDI parameters. However, TDI parameters had a significant difference with healthy subjects.

Systolic and diastolic LV dysfunction was similarly found in patients with AAMSF below and above 1000 ng/ml, consequently. No significant correlation was identified between the AAMSF level and TDI or PWD indexes.

In our study, systolic and diastolic ventricular dysfunctions were also demonstrated in patients with normal LVEF or LVFS.

We found insufficiently impaired cardiovascular function in B-TM patients, even with the AAMSF level below 1000 ng/ml. However, these patients did not present with clinical manifestations of cardiac failure.

As a result, AAMSF less than 1000 ng/mL has not been considered a safe cut off for subclinical systolic and diastolic cardiac function. Therefore, AAMSF levels should be maintained lower than 1000 ng/mL in patients with thalassemia by excellent chelation therapy.

In conclusion, our study has provided evidence for cardiac systolic and diastolic subclinical dysfunction in thalassemia patients, especially among patients with AAMSF levels above 1000 ng/ml. We suggest that in the thalassemia, patients were performed echocardiography by using TDI and PDW for assessment of subclinical cardiac dysfunction, and the TDI is more useful than PWD for subclinical cardiac evaluation. Also, we thought that the measurement of AAMSF Levels is a useful index for the prediction of cardiac subclinical systolic and diastolic dysfunction.

Our study has some limitations, including small sample size and absence long term follow up. A large random sample was required to distinguish the correlation between echocardiographic parameters and AAMSF levels. This was a preliminary study that attempted to establish a correlation AAMSF Levels and echocardiography in pediatrics suffering from major thalassemia. Our result is encouraging and should be validated by larger sample size and a long term prospective study on PWD and TDI for assessing subclinical cardiac function

Acknowledgments

We are grateful to the Thalassemia ward staff for their Kindly cooperation in collecting the data needed for analysis.

References

1. Muncie HL Jr, Campbell J. Alpha and beta thalassemia. Am Fam Physician 2009;80:339-44.
2. Aessopos A, Farmakis D, Hatziliami A, Fragodimitri C, Karabatsos F, Joussef J et al. Cardiac status in well-treated patients with thalassemia major. Eur J Haematol

2004;73:359-66.
3. Chrysohoou C, Greenberg M, Pitsavos C, Panagiotakos DB, Ladis V, Barbetseas J, et al. Diastolic function in young patients with beta-thalassemia major: an echocardiographic study. Echocardiography 2006;23:38-44.
4. Atig M, Bana M, Ahmed US, Bano S, Yousuf M, Fadoo Z et al. Cardiac disease in beta-thalassemia major: is it reversible? Singapore Med J 2006;47:693-6.
5. Ocal B, Oguz D, Karademir S, Birgen D, Yüksek N, Ertem U, et al. Myocardial performance index combining systolic and diastolic myocardial performance in doxorubicin-treated patients and its correlation to conventional echo/Doppler indices. Pediatr Cardiol 2002;23:522-7.
6. Eghbali A MD, Taherahmadi H, Bagheri B, Nikanjam S, Ebrahimi L. Association between serum ferritin level and diastolic cardiac function in patients with major β-thalassemia. Iran J Ped Hematol Oncol 2015,5:83-8
7. Kyriacou K, Michaelides Y, Senkus R, Simamonian K, Pavlides N, Antoniades L, et al. Ultrastructural pathology of the heart in patients with beta-thalassaemia major. Ultrastruct Pathol 2000;24:75-81 .
8. Roeser P, Halliday J W, Sizemore D J, Nikles A, Willgoss D. Serum Ferritin in Ascorbic Acid Deficiency. Br J Haematol 1980;45:459-66.
9. Shahmohammadi A, Davari P N, Aarabi Y, Meraji M, Tabib A, Mortezaeian H. Echocardiographic Assessment of Cardiac Involvement in Patients with Thalassemia Major: Evidence of Abnormal Relaxation Pattern of the Left Ventricle in Children and Young Patients. Arch SID 2006;7:13-19.
10. Modell B, Berdoukas V. The clinical approach to thalassemia. New York: Grune and Stratton, 1984:171.
11. Papadopoulou-Legbelo K, Varlamis S G, Athanassiou-Metaxa M, Karamperis S, Malaka-Zafiriou A. Full resting echocardiographic study of left ventricle in children with b-thalassemia major KAP¢IO§O°IA 2009; 2-3:132-8.
12. Hahalis G, Manolis AS, Apostolopoulos D, Alexopoulos D, Vagenakis AG, Zoumbos NC. Right ventricular cardiomyopathy in beta-thalassemia major. Eur Heart J 2002;23:147-56.
13. Öcal B, Oğuz O, Karademir S, Birgen D, Yüksek N, Ertem U, et al. Myocardial performance index combining systolic and diastolic myocardial performance in doxorubicin-treated patients and its correlation to conventional echo/Doppler indices. Pediatr Cardiol 2002;23:522-7.
14. Gharzuddine WS, Kazma HK, Nuwayhid IA, Bitar FF, Koussa SF, Moukarbel GV, et al. Doppler characterization of left ventricular diastolic function in beta-thalassaemia major. Evidence for an early stage of impaired relaxation. Eur J Echocardiogr 2002;3:47-51.