Original Article

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Brain Natriuretic Peptides and Calcitonin Gene-Related Peptide in Diagnosis of Cardiac Involvement in Major Thalassemia Patients

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Abstract

Background: Cardiac dysfunction is one of the major causes of morbidity and mortality in thalassemia patients. This study aimed to compare the effect of Brain Natriuretic Peptides (BNP) and Calcitonin Gene-Related Peptide (CGRP) with echocardiographic findings in early diagnosis of cardiac disease in major thalassemia patients.

Materials and Methods: This study was performed on 80 patients among 500 major thalassemia patients and 80 healthy people. Those with metabolic, endocrine disorder, hypertension, heart failure, and valvular disease excluded from the study. These two groups were matched based on age and sex. Essential heart findings were analyzed using Mylab 60. After blood sampling, levels of CGRP and BNP were measured by use of ELISA kit from extracted plasma. Mann-Whitney test, independent t-test, and Pearson correlation were used to analyze data and $P< 0.05$ was considered significant.

Results: The results showed that mean age of all participants was 17.581±5.344 years when distributed between case and control as 18.21 ±5.14 and 16.95 ±5.49 respectively without significant difference. Means of weight, length, hemoglobin, systolic and diastolic pressure were lower in patients group. The majority of echocardiography findings of left and right heart were higher in case group. The average of CGRP and BNP level were more in case group ($p<0.05$). A positive correlation was observed between BNP ($R=0.229$, $P=0.041$) and right MPI. There was also correlation between PEP($R=0.0238$,$P=0.035$) , PEP/ET($P=0.005$) of right heart and peak A velocity of left heart ($R=0.245$,$P=0.03$) with CGRP.

Conclusion: Findings of this survey showed that systolic and diastolic function of left heart would be changed in patients with major beta thalassemia. Therefore, monitoring BNP and CGRP in symptom free thalassemia patients as well as serial echocardiography is recommended.

Keywords: Brain Natriuretic Peptides, Calcitonin Gene-Related Peptide, Children, Echocardiography, Major thalassemia rt

Introduction

Thalassemia major is a common genetic disorder that causes severe anemia from early childhood. Annually 60000 to 100000 livebirth are born with thalassemia major worldwide. During the last three decades, the treatment of patients with multiple blood transfusions and systemic iron chelating agents has caused a significant improvement in the quality of life and life expectancy (1-3). Cardiac involvements are important causes of death in patients with major thalassemia. Iron overload is a reason for permanent and severe cardiac involvement especially for untreated anemia (2). Two broad spectrum of the thalassemia range from asymptomatic carriers to patients with dependent transfusion thalassemia major.

Chronic hypoxia and increased pulmonary with systemic vascular resistance are main factors of leading to heart disease in thalassemia. The cause of increased

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pulmonary vascular resistance in patients with beta thalassemia is multi-factorial(2). Systolic and diastolic dysfunctions that following hemosiderosis are main causes of early death for these patients(3).

In the other hand, the most common cause of death in major thalassemia patients is dilated cardiomyopathy accompanied by left ventricular dysfunction (4). Neurohormones are hormones which produced and released by neuroendocrine cells into the blood and Brain Natriuretic Peptides (BNP) is one of them that released from ventricular myocytes response to ventricular dysfunction and wall stress. Introduced BNP is broken to NT-Pro BNP in circulation(5). BNP and NT-pro-BNP are extensively used for heart failure diagnosis. These peptides may be useful for screening asymptomatic high risk patients such as patients with hypertension, diabetes mellitus, coronary artery disease, and thalassemia(6). A plasma BNP decrease is occurring in the first week of life (7). The level of NT-Pro BNP is increasing in major beta thalassemia patients compared to healthy. This increase is due to age and left ventricular dysfunction and it is a biomarker to determine the left ventricular dysfunction compared with doppler echocardiography in thalassemia patients (8). CGRP has positive inotropic and chronotropic effects on the heart and is also considered the most potentially endogenous peptide. Previous reports on the changes of CGRP in congestive heart failure (CHF) are varied and poorly spoken bout regulation of CGRP production(9). Unfortunately, inconsistent reports are exist about the effects of CGRP on CHF with various conditions that increased the levels of CGRP such as pregnancy, hepatic cirrhosis or hemodialysis (5). However, in infants and children the most common etiology of CHF is CHD and increasing pulmonary blood flow plays an important role in the pathogenesis in CHF to secondary CHD. CGRP is the most important vasodilator with positive inotropic effects and the most potent vasoconstrictor in vessels (9,10). In hemodialysis patients, the plasma levels of CGRP are significantly higher in patients with fluid excess and are correlated with the degree of fluid overload (9-10). The level of calcitonin of plasma increases in left to right shunts and it would be a reason of moderating the severe of pulmonary hypertension (10). Because the number of investigations in the role of CGRP and BNP in diagnosis cardiac involvements in thalassemia patients is low, the present study aimed to assess the role of CGRP and BNP in early diagnosis of cardiac involvement in asymptomatic major thalassemia patients with respect to control group.

Materials and Methods

This study was performed on 80 patients in age ranged of 10-25 years selected randomly among 500 major thalasemic patients who referred to Aliasghar center during March 2014 to March 2015. Same numbers were selected from healthy people who referred to the center for routine checkup. Sample size was based on the cost, age, and many ethical limitations for controling participants .These two groups of participants were matched in terms of age and sex to reduce the impact of probably interpositions. Major proceedings were performed on both case and control groups such as medical history, physical examination, chest X-Ray, and Electrocardiogram (ECG) before echocardiography as well Echocardiography was performed by the same cardiologist. Essential parameters which had been analyzed in both groups were as follows: Deceleration time(DT) ,Myocardial Performance Index(MPI) ,peak E velocity/peak A velocity (E/A),Isovolemic contraction time(ICT), Isovolemic relaxation time(IRT), Interventricular septal dimension in systole(IVSS), Interventricular septal dimension in diastole(IVSD),Left ventricular end-diastolic

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dimension(LVDD),Fractional Shortening (FS),Ejection Fraction(EF), Left ventricular end-systolic dimension(LVSD), Left ventricular posterior wall dimension in diastole(LVPWD), Left ventricular posterior wall dimension in systole(LVPWS), Acceleration Time(AT), Left ventricular mass index(LVMI). From all participants, those who had metabolic disorders, endocrine disorders, hypertension, heart failure, and valvular disease excluded from the study. Echocardiography was performed on patients 48-72 hours following packed red blood cell transfusion by same pediatric cardiologist using My lab 60 with transducer 3-8 made in Italy. For more precision echocardiography was repeated in 3 different cycles of 2D, M-Mode, and Doppler methods and considered the average. Echocardiogram applied in supine position and without breath holding and view was taken in the mitral valve surface in parasternal position. Systolic and diastolic interventricular diameter, diameter of left ventricular posterior wall, end Systolic and diastolic measurement of left ventricle and ejection fraction were also calculated with M-mode. Pulsed Doppler was used to determine blood velocity and pre ejection period Ejection time, peak A velocity, Pak E velocity and Ejection time and then E/A,PEP/ET were calculated. Before blood samplings, patients were asked to rest for 15 minutes and then 5 cc of blood sample was taken and centrifuged at 3000 rpm/min about 10 minutes. Then, provided samples were stored at minus 80c. This process performed for both case and control groups. Finally, calcitonin and BNP were measured by ELISA kit (USA). To measure “a” the sample volume was positioned at the tips of the tricuspid and mitral valve leaflets in the apical four-chamber view which is defined as the time of interval between the end and the start of trans-mitral and trans-tricuspid flow. To measure “b”, the sample volume was placed to the left ventricular out flow tract just below the aortic valve in apical five-chamber view which is defined as the left ventricular ejection time. For the right ventricular outflow, velocity pattern was also recorded from the parasternal short-axis view with the Doppler sample volume positioned just distal to the pulmonary valve. MPI or the Tie Index was calculated as: a-b/b = IRT + ICT/ ET. The left ventricular mass index (LVMI) was also calculated by equation of LVMI = 0.8 *(1.04) (LVIDD + PWTD + IVSTD)**3-(LVIDD)**3 + 0.6 8. Measures recorded in a specific sheet and entered to the SPSS 20 (SPSS, Inc., Chicago, IL) and analyzed based on proper statistical tests. Kolmogorov-Smirnov test was used for normality. If the distribution of data was normal, parametric tests and in contrast non-parametric were used. Mann-Whitney test, independent t-test, and Pearson correlation were the applied tests with significant level of < 0.05.

Results

Sex distribution was 52.5% male and 47.5% females in case group and 50% male and 50% female in control. Weight, heigh,t and hemoglobin means were significantly higher in control (50.2 ±15.9, 158.47 ± 15.47 and 14.32 ±1.09) compared to case (38.21 ±8.82, 145.83 ±12.3 and 10.37 ±0.34) group in the level of $p<0.001$(Table 1). Table II shows the results of the test of normality for the principal variables. Test of K-S revealed that the majority of variables were distributed normally such as PEP/ET (K-S=1.041, p=0.229), LVMI (K-S=795, p=0.553) and LVDD (K-S=0.943, p=0.336) and the minority of variables were non-normal such as BNP (K-S=4.952, $p<0.001$), and CGRP (K-S=, 1.660 p=0.008). Table III shows the results of independent t-test comparing case and control groups for those variables with normal distribution. The Table reports no statistically significantdifference for echocardiographic findings such as

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Ventricular posterior wall dimension in diastole (p=0.317), Interventricular septal dimension in systole (p=0.536), Ventricular posterior wall dimension in systole (p=0.058), Peak A velocity (p=0.375), and Peak E velocity in right (p= 0.112) when for the some findings such as PEP/ET in left (p<0.001), ET in right (p<0.001) and PEP/ET in right(p<0.001) the differences were significant. Table 4 reveals the results of non-parametric Mann Whitney U test comparing case and control groups for those variables with non-normal distribution. The result revealed that right MPI (Mean Rank= 41.675 for control and Mean Rank= 119.325 for patients with p<0.001), left MPI (Mean Rank= 45.275 for control and Mean Rank= 115.725 for patients with p<0.001), PEP in left (Mean Rank= 65.7 for control and Mean Rank= 95.3 for patients with p<0.001) and ET in left (Mean Rank= 96.03 for control and Mean Rank= 64.97 for patients with p<0.001) had different significant mean rank in case and controls. Meanwhile, some of Echocardiographic findings demonstred no differences in case and controls such as Interventricular septal dimension in diastole (Mean Rank= 78.36 for control and Mean Rank= 82.64 for patients with p=0.556) and right DT (Mean Rank= 86.01 for control and Mean Rank= 74.99 for patients with p=0.130). Table 5 depicts the correlation of BNP and CGRP as biomarkers with right and let echocardiography findings in both groups and all population in the study. In case group, the findings showed that BNP had a significant correlation with right MPI (r= 0.229, p=0.041) and CGRP had significant correlations with PEP in right (r= 0.238, p=0.035), PEP/ET in right (r= 0.316, p=0.005), and peak A velocity in left(r= 0.245, p=0.030).

Table I: Anthropometric and Hemoglobin mean in case and control

Variable	Mean ±sd (participants)	Mean ±SD (patients)	Mean ±SD (control)	P value(for case and controls)
Age(year)	17.581±5.344	18.21 ±5.14	16.95 ±5.49	0.136
Weight(kg)	44.206±14.161	38.21 ±8.82	50.2 ±15.9	0.0001
Height(cm)	152.156±15.313	145.83 ±12.3	158.47 ± 15.47	0.0001
hemoglobin(g/dl)	12.352 ±2.138	10.37 ±0.34	14.32 ±1.09	0.0001

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Table II: Results of Kolmogorov-Smirnov test for normality

parameters	Mean	sd	K-S	p	parameters	Mean	sd	K-S	p
PEP/ET (L)	0.34	0.051	1.041	0.229	ICT (R)	38.369	21.059	0.877	0.426
ET (R)	261.719	23.189	1.264	0.082	Peak E (R)	59.5	13.511	1.05	0.22
PEP/ET (R)	0.34	0.051	1.053	0.218	Peak A (R)	44.206	10.172	1.346	0.053
PWD (L)	4.672	0.809	1.318	0.062	MPI (R)	0.553	0.17	1.858	0.002
IVSS (L)	11.196	1.742	1.041	0.229	MPI (L)	0.517	0.13	1.782	0.003
PWS (L)	5.444	0.872	1.212	0.106	PEP (L)	89.644	10.347	2.107	0.000
LVDD (L)	47.654	5.251	0.943	0.336	ET (L)	263.294	23.736	1.323	0.06
LVEDV (L)	69.481	20.585	0.594	0.873	PEP R	89.306	10.696	2.446	0.000
LVMI (L)	75.212	22.499	0.795	0.553	IVSD (L)	8.195	1.396	1.533	0.018
EF (L)	68.45	6.056	0.953	0.324	LVDS (L)	29.501	4.659	1.516	0.02
FS (L)	38.444	5.758	1.015	0.254	IRT (L)	103.481	18.512	1.497	0.023
LA	26.788	4.258	0.954	0.322	AT (L)	60.506	13.036	2.706	0.000
Aorta	24.559	3.463	1.091	0.185	IRT (R)	113.613	23.67	1.392	0.042
LA/ Aorta	1.096	0.173	1.317	0.062	AT (R)	64.631	16.168	2.593	0.000
ICT (L)	33.556	21.462	1.156	0.138	DT (R)	141.606	20.987	1.717	0.005
DT (L)	143.863	22.096	1.163	0.133	E/A (R)	1.372	0.307	1.432	0.033
Peak E (L)	91.781	17.412	0.929	0.354	BNP	6.309	18.918	4.952	0.000
Peak A (L)	50.913	11.712	1.084	0.191	CGRP	3.784	2.906	1.66	0.008
E/A (L)	1.863	0.461	0.96	0.316	age	17.581	5.344	0.925	0.36

L= left heart , R = Right heart, PEP = Pre-ejection Period (m/s), ET = Ejection Time (m/s),PWD=Posterior wall dimension in diastole (mm),IVSS=Interventricular septal dimension in systole (mm), PWS=Posterior wall dimension in systole (mm),IVSD= Interventricular septal dimension in diastole (mm),LVDD=Left ventricular dimension diameter in diastole (mm),LVDS=Left ventricular dimension diameter in systole (mm), LVEDV= Left ventricular end diastolic volume(mm),LVMI= Left ventricular mass index (mm),EF= Ejection Fraction , FS= Fractional Shortening, LA=Left atrium,ICT= Isovolemic contraction time (m/s), DT = Deceleration time(m/s), MPI = Myocardial performance index, AT= Acceleration time (m/s), IRT= Isovolemic relaxation time, E/A =peak E/peak A velocity, BNP= Brain Natriuretic Peptides (pg/ml), CGRP= Calcitonin gene-related ptide(µg/l).

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Table III : Results of independent t- test for normal variables in comparison in case and control groups

variables for the left Heart	group	Mean	SD	t	P
Pre-ejection period	control	0.316	0.038	-6.896	**<0.001**
	case	0.365	0.051		
Pre-ejection period/ejection time	control	0.316	0.039	-6.792	**<0.001**
	case	0.364	0.05		
Ventricular posterior wall dimension in diastole	control	4.736	0.869	1.005	0.317
	case	4.608	0.744		
Interventricular septal dimension in systole	control	11.11	1.645	-0.62	0.536
	case	11.281	1.841		
Ventricular posterior wall dimension in systole	control	5.575	0.839	1.909	0.058
	case	5.314	0.891		
Ventricular end-diastolic dimension	control	46.834	5.479	-1.994	**0.048**
	case	48.474	4.911		
Ventricular end-diastolic volume	control	63.32	18.166	-3.957	**<0.001**
	case	75.642	21.118		
Left ventricular mass index	control	66.067	17.058	-5.613	**<0.001**
	case	84.356	23.633		
Ejection Fraction	control	69.163	5.995	1.494	0.137
	case	67.738	6.071		
Feactional shortening	control	38.813	5.222	0.809	0.42
	case	38.075	6.26		
Left atrium	control	25.268	3.795	-4.82	**<0.001**
	case	28.308	4.173		
Aorta	control	24.928	3.759	1.348	0.18
	case	24.191	3.119		
Left atrium / Aorta	control	1.02	0.125	**-6.27**	**<0.001**
	case	1.173	0.18		
Isovolumic contraction time	control	23.338	16.285	-6.834	**<0.001**
	case	43.775	21.221		
Deceleration Time	control	149.813	23.675	3.527	**0.001**
	case	137.913	18.719		
Peak E velocity	control	88.95	16.894	-2.078	**0.039**
	case	94.613	17.565		
Peak A velocity	control	51.738	12.921	0.89	0.375
	case	50.088	10.38		
E/A velocity ratio	control	1.775	0.405	-2.463	**0.015**
	case	1.951	0.498		
	control				
variables for the right heart	case	Mean	SD	t	P

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Isovolumic contraction time	control	31.3	17.993	-4.495	**<0.001**
	case	45.438	21.625		
Peak E velocity	control	57.8	12.928	-1.599	0.112
	case	61.2	13.943		
Peak A velocity	control	42.513	9.317	-2.129	**0.035**
	case	45.9	10.753		
Ejection time	control	268.238	21.269	3.695	**<0.001**
	case	255.2	23.321		

Table IV: Results of non-parametric Mann-Whitney U test for non-normal variable

Variables for the left heart	**groups**	**Mean Rank**	**Sum of Ranks**	**Mann-Whitney U**	**p**
Myocardial performance index	control	45.275	3622	382	**<0.001**
	case	115.725	9258		
Pre-ejection period	control	65.7	5256	2016	**<0.001**
	case	95.3	7624		
Ejection time	control	96.03125	7682.5	1957.5	**<0.001**
	case	64.96875	5197.5		
Interventricular septal dimension in diastole	control	78.35625	6268.5	3028.5	0.556
	case	82.64375	6611.5		
Interventricular septal dimension in systole	control	73.1375	5851	2611	**0.044**
	case	87.8625	7029		
Isovolumic relaxation time	control	59.3875	4751	1511	**<0.001**
	case	101.6125	8129		
Variables for the right heart and biomarkers	groups	Mean Rank	Sum of Ranks	Mann-Whitney U	p
Myocardial performance index	control	41.675	3334	94	**<0.001**
	case	119.325	9546		
Pre-ejection period	control	63.9	5112	1872	**<0.001**
	case	97.1	7768		
Isovolumic contraction time	control	50.7125	4057	817	**<0.001**
	case	110.2875	8823		
Acceleration time	control	74.44375	5955.5	2715.5	0.091
	case	86.55625	6924.5		
Deceleration time	control	86.00625	6880.5	2759.5	0.130
	case	74.99375	5999.5		
Peak E/A velocity ratio	control	83.01875	6641.5	2998.5	0.492
	case	77.98125	6238.5		
Brain Natriuretic Peptide	control	73.1125	5849	2609	**0.043**
	case	87.8875	7031		
Calcitonin gene-related peptide	control	57.5	4600	1360	**<0.001**
	case	102.7848	8120		

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Table V: Results of biomarkers correlation with echocardiography findings in Patients

Right echo findings	**statistics**	**Case group (Patients)**		**Left Echo findings**	**Case group(Patients)**	
		BNP	CGRP		BNP	CGRP
ICT	PC	0.200	0.085	MPI	0.212	0.087
	p	0.076	0.456		0.059	0.445
IRT	PC	-0.052	-0.114	PEP	-0.065	0.068
	p	0.650	0.315		0.566	0.553
AT	PC	-0.059	-0.001	ET	-0.187	-0.097
	p	0.602	0.991		0.097	0.396
PEP/ET	PC	-0.022	0.316	PEP/ET	0.071	0.115
	p	0.848	0.005		0.534	0.313
DT	PC	0.152	0.184	IVSD	-0.022	0.007
	p	0.179	0.104		0.847	0.954
E	PC	-0.024	0.106	PWD	0.012	-0.017
	p	0.830	0.351		0.913	0.879
A	PC	0.023	0.014	IVSS	-0.025	0.067
	p	0.842	0.902		0.828	0.556
A/E	PC	-0.041	0.134	PWS	0.034	0.020
	p	0.721	0.241		0.764	0.864
MPI	PC	0.229	0.052	LVDD	0.104	0.072
	p	0.041	0.648		0.360	0.530
PEP	PC	-0.040	0.238	LVDS	0.072	0.032
	p	0.724	0.035		0.528	0.780
ET	PC	-0.030	-0.153	LVDV	0.099	0.098
	p	0.795	0.178		0.385	0.392
Left Echo findings	PC	Case group(Patients)		LVMI	0.013	-0.010
	p	bnp	CGRP		0.910	0.933
AT	PC	0.010	0.126	FS	0.035	0.002
	p	0.932	0.270		0.759	0.987
EF	PC	0.058	0.041	LA	0.048	0.165
	p	0.613	0.720		0.673	0.147

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DT	PC	-0.078	0.105	Aorta	0.110	0.029
	p	0.495	0.357		0.331	0.801
E	PC	-0.075	0.011	LA/ Ao	-0.046	0.118
	p	0.510	0.923		0.683	0.303
A	PC	-0.039	0.245	ICT	0.116	0.080
	p	0.729	0.030		0.305	0.486
E/A	PC	-0.040	-0.167	IRT	0.039	0.020
	p	0.725	0.142		0.733	0.863

PEP =Pre-ejection Period , ET =Ejection Time, PWD= Posterior wall dimension in diastole, IVSS= Interventricular septal dimension in systole , PWS= Posterior wall dimension in systole , IVSD == Interventricular septal dimension in diastole ,LVDD= Left ventricular dimension diameter in diastole , LVDS = Left ventricular dimension diameter in systole, LVEDV= Left ventricular end diastolic volume , LVMI= Left ventricular mass index ,EF= Ejection Fraction , FS= Fractional Shortening , LA=Left atrium , ICT= Isovolemic contraction time , DT = Deceleration time , MPI = Myocardial performance index , AT= Acceleration time , IRT= Isovolemic relaxation time , E/A =peak E/peak A velocity, BNP= Brain Natriuretic Peptides, CGRP= Calcitonin gene-related peptide.

Discussion

The analysis of the present study showed that means of weight, height, and hemoglobin were higher in control compared to case. BNP and CGRP levels had higher mean ranks in case compared to controls. Accordance with correlation analysis, it was observed that the level of BNP had a significant correlation with right MPI in patients but CGRP had significant correlation with more echocardiographic findings such as PEP, PEP/ET in right heart and peak A velocity in left heart. Kremastinos reported that NT-Pro BNP was increased in major beta thalassemia patients compared to controls and this increase in patients was likely due to age and left ventricular diastolic dysfunction (11) but Whal held that BNP increasing was a reflection of preload volume and afterload pressure which release hormones in response to cardiomyocytes stretch (12)because of choosing asymptomatic patients in the present study and comparing different biomarkers compared to Kremastinos and Whal studies, the results could be comparable. Hamodraka observed that both BNP and NT Pro BNP would be increased in major beta thalassemia patients with systolic and diastolic dysfunction (13). In the present study, an increase of BNP in major beta thalassemia patients with diastolic and systolic dysfunction resulte was similar with the mentioned study regarding BNP. Aessopos and Meloni demonstrated that cardiac effects were the main causes of mortality in major beta thalassemia patients and BNP level increases in patients with global or local left ventricular diastolic dysfunction due to wall stretch in left ventricle (14,15). Direct correlation was found between MPI of right heart and BNP in patients. This result revealed that BNP was a good biomarker in early diagnosis of heart involvement in thalassemia patients. Tanner showed that myocardial sidrosis occurred in two third of thalassemia patients who were treated with deferoxamine and BNP was not a valuable biomarker to evaluate myocardial sidrosis (16) which somehow was dissimilar with

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the present study results regarding myocardial sidrosis.

In Aessopos study had been explained that forecasted the risk of heart failure progress by BNP and it would be increased in patients with obvious cardiac dysfunction but did not show the severity of failure (17). Maisel study showed that Pro BNP was useful like BNP in diagnosis of heart failure with dyspnea and acute heart failure (18). In the present study, patients were asymptomatic which was different with Aessopos and Maisel researchers that had been performed on patients with heart failure. Therefore, with respect to this different, it was found that BNP and Pro BNP were useful tools to diagnosis of cardiac involvement in patients with major thalassemia. Xin conducted a study on the relationship between echocardiographic findings and CGRP of right heart and observed that CGRP level had indirect correlation with ventricular MPI and pulmonary hypertension (19). There was no relationship between CGRP level and ventricular MPI in major thalassemia patients in the present study but a strong relationship with PEP, PEP/ET in right heart and Peak A velocity in left were observed. Marangoni were analyzed a few diabetic rats by injecting streptozotocin (STZ) to them. Then LVDD, LVSD, IVSD, IVSS, FS, E/A, IVRT, and DT were measured and observed that these echocardiographic findings were lower in controls compared to cases (20). The present study came to the conclusion that LVDD, E/A, IVRT were lower in control group similar to Marangoni study. Main differences between these two studies were related to the subjects and causes of cardiac involvement. Suman expressed that MPI was very high in chelated thalassemia children which can be used as an early biomarker to diagnose ventricular dysfunction (21). Along with Suman outcomes on chelated thalassemia children, a few reports revealed that the prognoses of patients with elevated BNP levels were consistently poorer in quality and low active life expectancy in compared with patients in lower BNP levels. This consistency was due to the presence of LV diastolic dysfunction in thalassemia major (22, 23). Therefore, BNP levels were used to predict the prognosis of patients with cardiovascular disease, particularly in patients with LV diastolic dysfunction. Hsu measured CGRP levels in CHD patients and concluded that an increase of CGRP level would be associated with pulmonary hypertension (9). In CHD patients, a main causes of CHF (Congestive Heart Failure) were volume overload and volume pressure. In major thalassemia patients, cause of cardiac dysfunction was iron overload with regarde to the immunologic factors. In compared with the present study, Hsu did measured CGRP on CHD patients whereas in this study CGRP was measured in asymptomatic patients with major thalassemia. Anand evaluated the impact of CGRP on cardiovascular system in animals with heart failure. After CGRP injection, cardiac output increased and vascular resistance decreased. Overall, Anand's study showed that CGRP was a potent vasodilator and could have effects on ventricular myocardium. Thus, it was suggested that CGRP could be used for treatment of heart failure (24). The difference between Anand's study and the present was related to the samples under investigation (animal models instead of humans). A study on the impact of CGRP on heart contractility and hemodynamic in idiopathic dilated cardiomyopathy patients revealed that after CGRP injection, norepinephrine increased but blood pressure decreased. Hence, CGRP can be recommended for the treatment of heart failure (25). Noori performed a study on dilated cardiomyopathy patients and showed that severity of illness based on the Ross classification had positive correlation with BNP and BNP had a significant correlation with majority of echocardiographic parameters (8). With respect to this fact that the majority of

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thalassemia patients suffere from type of cardiomyopathy and the association between these two diseases, the results of the present study would be in line with Noori's study.

Conclusion

The majority of echocardiography findings were increased in the thalassemia patients compared to controls. Biomarkers of CGRP and BNP were increased in patients with major thalassemia compared to controls. These biomarkers had significant correlation with some of echocardiography findings such as MPI, PEP/ET, and PEP in right heart and Peak A velocity for the left heart. Hence, it seemed that CGRP and BNP can be useful in early diagnosis of cardiac involvement in patients with major thalassemia. In addition, it was found that BNP can be a stronger biomarker than CGRP .

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Conflict of interest

The authors would like to declare no conflict of interests.

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