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TNF-α, INTERLEUKIN-6, NT-PRO BNP CORRELATION WITH ECHOCARDIOGRAPHY FINDINGS IN PATIENTS WITH THALASSEMIA

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Contribution

NMN conceived the idea and did statistical analysis. MNM did data collection. AT and MI did review and final approval of manuscript. All authors contributed equally to the submitted manuscript.

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ABSTRACT

Objective: To investigate the possible relationship between TNF-α, Interleukin-6, NT-pro BNP, leptin and ferritin with echocardiography findings in thalassemia patients compared to controls.

Methodology: This case control study was performed on patients and controls from 1st January to 31st December, 2017. Blood samples were taken from participants in fasting to measure Leptin, Ferritin, TNF-α, NT-pro BNP and IL-6 serums. Participants underwent echocardiography by pediatric cardiologist. The level of error considered as 0.05 for data analysis by SPSS version 20.0.

Results: There were 112 cases and 114 controls. Mean age of participants was 16.09±7.11 years. NT-pro BNP, TNF-α, IL-6, and Ferritin were different in patients compared to control but leptin was same. Left DT was higher in patients. All echo modalities including A and E, doppler velocities, EF, FS, heart rate, left Peak E/A, right Peak E/A , LA/Ao in diastole, and in systole ,LVMI, MPI left, MPI right and BMI were different in patients and controls($p<0.05$). In patients, NT-pro BNP, leptin, TNF-α, Interleukin and ferritin did not correlate to each other except TNF-α and IL-6($p=0.001$).

Conclusion: NT-pro BNP, TNF-α, IL-6, Ferritin were higher in cases and they correlated with some of echocardiography findings whereas leptin was same in case and controls and correlated with ECG findings only. The findings of the study suggested that NT-pro BNP maybe the best bio marker for evaluation of cardiac function in thalassemia patients.

Key Words: Evaluation, Conventional echocardiography dysfunction, Beta Thalassemia, Children

INTRODUCTION

Haemoglobinopathies are the most common inherited genetic disorders involving an abnormality in the structure of thalassemia and hemoglobin. Large number between 300,000 and 400,000 babies are born with a serious hemoglobin disorder each year and that up to 90% of these births occur in low or developing nations and from those, new born with thalassemia accounted from 60,000 to 100,000.[1,2] Thalassemiais prevalent worldwide but is more common in sub-Saharan Africa, South-East Asia and the Mediterranean belt.[1,3] Iran in Middle East with different parts has approximately 25,000 thalassemia patients and three million carriers. Two Persian Gulf and the Caspian Sea regions have more than 10 percentages and Sistan and Baluchestan province has 4 to 10%.[1] The clinical phenotypes of thalassemia ranged from the asymptomatic carrier (thalassemia minor), with no obvious clinical manifestations, to the severely affected patient (thalassemia major), with profound anemia and skeletal deformities necessitating regular transfusions for survival.[4] Sistan and Baluchestan province of Iran, have thalassemia gene frequency which deals about high numbers of patients with major beta thalassemia who are receiving regular health services such as blood transfusion.[1,3,5] One of the most important organs that impressed by iron overload is heart especially in thalassemia patients. The main causes of thalassemia cardiomyopathy are increasing intestinal absorption, hemolysis and lifelong blood transfusions determine myocardial iron overload.[6]

Natriuretic Peptides (Nps), have been considered as diagnostic biomarkers for cardiovascular diseases, and they contain of B-type natriuretic peptide (BNP), prohormone brain natriuretic peptide (pro BNP).Both BNP and ProBNP can be measured by fully automated which have proven excellent test precision. BNP and NT-ProBNP plasma concentrations are expressed in pg/ml or pmol/l and it is proven that NT-Pro BNP is more stable with longer half-life about 2 hours in compare to BNP.[7] In the early phases of the cardiac involvement, the level of NT-Pro BNP increases before an increase occurred in diastolic pressure because of a strong relationship between NT-pro BNP and iron overload in which due to this fact, a significant association between NT-pro BNP, and some diastolic dysfunctions has been observed.[8,9] On other hand, an increase level of NT-pro BNP can be used as a tool for primary detection of cardiac hemosiderosis, and is confirmed iron chelation therapy, which may reverse iron-induced cardio-myopathy.[1]

Cytokines have great immunologic actions and are considered important catabolic factors.[5] Among cytokines, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are secreted secondary to several chronic diseases. In addition, they play a major role in cardiac cachexia and exacerbate prognosis.[5]

TNF-α is a cytokine with a large variety of properties that is involved in the activation of endothelial cells and leukocytes. It plays an important role in the synthesis of acute phase proteins and in the expression of adhesion molecules by the vascular endothelium.[1] In sickle cell anemia, TNF- α has been linked as a risk factor for the occurrence of painful crises, as well as participating in the occlusion of the microcirculation.[7]

Moreover, pro-resorptive levels of TNF-α and IL-6 are elevated in patients with thalassemia. These inflammatory cytokines inhibit growth plate proliferation and differentiation, increase apoptosis and cause reduction in matrix synthesis and impairment of local insulin-like growth Factor-I (IGF-I) signaling.[10]

Leptin is a polypeptide of 146 amino acids that issued widely in different tissues. This hormone is multi-functional and leads to increase energy levels and affects angiogenesis, inflammation, and hematopoiesis.[8]

Leptin acts on the hypothalamic receptors and influences the expression of different neuropeptides that regulate energy balance by decreasing food intake and increasing energy expenditure and sympathetic tone in response to normal weight gain.[9]

Ferritin is a blood cell protein that contains of Iron. It is the best and the most common test specially in beta thalassemia major. The test is easy to perform compared with other tests for iron overload.[11] Iron is stored routinely which can cause harm various body organs. Iron may deposit in all layers of the heart but the deposits are more likely to occur in the external layer (epicardium) than the internal layer (endocardium). Deposition of iron in myocardium can cause both hypertrophy and dilated heart chambers.[12]

Several studies have demonstrated that there is an association between NT -Pro BNP (1), TNF-α ,Interleukin-6 leptin levels 9 and ferritin with heart findings in thalassemia patients.[5-7,9,11,13] In addition, has been reported that QTcd and QTd are good parameters of ECG that are associated with echocardiographic measurements such as left ventricular mass index (LVMI) in patients with thalassemia compared to controls.[2] In respect to abnormalities in thalassemia patients and the effects of TNF-α ,Interleukin-6, NT-Pro BNP, leptin and ferritin echocardiography findings, the present study aimed to investigate the possible relationship between these cytokines and biomarkers with echo findings in thalassemia patients compared to controls in Sistan and Baluchestan province of Iran.

METHODOLOGY

This case control study was performed on patients and controls from 1st January to 31st December, 2017.

All thalassemia patients who had regular transfusions to maintain pre-transfusion hemoglobin with the levels higher than 10 g/dL entered to the study.

Exclusion criteria were valvular disease, rhythm and structural abnormality, active infection, systemic inflammatory diseases, renal insufficiency, and these criteria were considered for both groups.

Major proceedings in patients were checking medical history, physical examination, chest X-ray and Electrocardiogram (ECG) that performed before echocardiography in which performed by paediatric cardiologist.

ECG findings were as follow: QT: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. QTc : QT / √ RR. NFQTc : (new formula for QTc in which is equal to 2qt/(1+RR). QTd : the difference between the

maximum and minimum QT values. QTcd : the difference between the maximum and minimum QTc values. NFQTcd : (new formula for QTcd in which is equal to 2qtd/(1+RR). Rv5: (R wave in V5) the amplitude of R wave in left Precordial. Sv1: (S wave in V1) the amplitude of S wave in right Precordial lead. All cases and controls underwent simultaneous 12-leads standard (made in Japan).[1,3,15]

Echocardiography was performed 48-72 hours after packed red blood cell transfusion on patients by same pediatric cardiologist with using of My lab 60 with transducer 3, 8 (made in Italy).

For having high precision in information echocardiography repeated 3 cycles in 2D, M-Mode, Doppler method and the average was considered.

Echocardiogram applied in participants without breath holding, and view was taken in the mitral valve surface in parasternal position.

Echocardiography findings were as follow LVDD: left ventricular end-diastolic dimension, AT: Acceleration time, DT: deceleration time, Peak E: early mitral and tricuspid valve flow velocity, Peak A: late mitral and tricuspid valve flow velocity, LAd: Diameter of LA in Diastole, Aod: Diameter of Aorta in Diastole, LAs: Diameter of LA in Systole, Aos: Diameter of Aorta in Systole, Et: ejection time (for Aorta and Pulmonary), PWDD: posterior wall dimension in diastole, IVSD: interventricular septal dimension in Diastole, IVSS: interventricular septal dimension in systole, EF: ejection fraction, FS: fractional shortening, LVM: left ventricular mass, RWT: relative wall thickness, LVMI: left ventricular mass index, were measured using conventional echocardiography of the left side were estimated from three cardiac cycles. Myocardial performance index (MPI), isovolumic relaxation time (IRT), isovolumic contraction time (ICT) of both sides, were measured with pulsed Doppler echocardiography.[15] The sample volume was positioned at the tips of the tricuspid and mitral valve leaflets in the apical four-chamber view to enable the measurement of (a): that is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow. The sample volume was thereafter relocated to the left ventricular outflow tract just below the aortic valve (apical five-chamber view), so as to measure (b): which is the left ventricular ejection time. 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 for the measurement of (b). Myocardial Performance Index (Tei Index), was calculated as: a-b/b = IRT + ICT/ET. The left ventricular mass index (LVMI), was also calculated by the following formula: LVM (g) = 0.8 (1.04 [LVEDD + PWTD + IVSTD)3 - LVEDD 3]) + 0.6. And LVMI (g/m2) = LVM / 2.7 (g/m2).

All the parameters in the above formula were measured in the M-mode view and in diastole and were utilized for left ventricular mass evaluation.[16] Relative Wall Thickness (RWT), was calculated as 2 times PWD divided by the LVEDD.[16]

From all participants, 5 cc blood was drawn at 8:00 am. Samples were centrifuged at 3000 g for 10 minutes at 5 °C. Separated serum was kept at -70 fridges till measuring NT -Pro BNP, TNF- α, Interlukin-6, ferritin and leptin. The samples transferred to the Biochemistry lab of Zahedan University of Medical Sciences (ZaUMS) under the cold chain, Then, 250 microns was isolated from serum samples for each measure in order to analyze ferritin by ELISA method/kit (US) and leptin level by ELISA method Kit (Canada).The levels of serum NT-Pro BNP, TNF-α and IL_6were measured by Eliza method with a KIT of Bender Med Company made of America.

Children's height and weight were measured. The recumbent length for children were graded using a flat wooden table and weight measurements for children were performed by using balance weights Mika with difference of 100gr. Then BMI was calculated with (Kg / m^2) (weight in kilograms divided by height to the power of 2) formula.

Consent form was obtained from the participants or their guardians after the study approval. The present study was a segment of an approved project proposed to the Children and Adolescent Health Research Center and approved by the Ethics Committee of ZaUMS, Iran (ID number: 6798).

Data analyzed by SPSS 18.0 (SPSS Inc, Chicago, IL, USA). Data reported as mean ± standard deviation (SD) for continuous variables or percentage for categorical variables. Differences between the two groups were evaluated with t-tests or Mann-Whitney U test and the correlation between the variables was determined using the Pearson coefficient. A $p<0.05$ was considered statistically significant.

RESULTS

The test normality performed on the variables of the study and showed that all the variables had not normal distribution. For the reason non-parametric tests were applied. Sex distribution in participants regarding gender as shown in table 1. Of 226 participants, 114 were healthy children and 112 were patients. From the participants, 101 were female. The distribution of females among case and controls were 48.5% and 51.5% respectively. The chi square test resulted that the sex distribution was similar and showed that participants were matched based on gender ($X^2= 0.27$, $p= 0.602$). Participants age ranged from 5 to 30 years with the mean of 16.09±7.11 years. The participant's age was distributed similarly in case and controls ($t=-1.418$, $p=0.158$).

NT-proBNP mean had different levels in case (439.79±817.57) and control (93.11±164.56) significantly ($p<0.001$) (Table 2). Case and control's participants had similar levels of leptin ($p>0.005$). TNF-α ($p<0.001$), Interleukin 6 ($p<0.001$), Iron($p<0.001$) and Ferritin ($p<0.001$) were different in case and controls so that all were significantly higher in case group (Table 2). The indices of height and weight were also different in case and control significantly ($p<0.001$) in favor of controls in the terms of higher levels.

Comparison of echo findings in groups of participants as shown in table 3. The table revealed that many of these finding was different in groups significantly. Left a, had higher values in patients (427.49±44.95) compared to controls(419.84±38.36) ($p=0.017$). Left DT had higher value in case ($p=0.008$), Left Peak A ($p=0.015$), right a ($p<0.001$), right peak E($p=0.032$), right peak A ($p=0.048$), Right ET ($p<0.001$), Lad ($p<0.001$), Las ($p<0.001$), Left ET ($p<0.001$), IVSD ($p=0.004$), LVDD ($p=0.024$), LVDS($p<0.001$), PWS ($p<0.018$), EF

MOD(p<0.001), FS (p<0.001), Simpson LVSD (p=0.018), Simpson EF (p=0.001), QT (P<0.001), Qtc (p<0.001), NF-QTc (p=0.001), NF-QTcd (p=0.002), Hear Rate(p<0.001), left Peak E/A (p<0.001), right Peak E/A (p=0.001), LA/Ao in diastole (p<0.001), BMI (p<0.001), LA/Ao in systole (p<0.001), LVMI (p=0.005), MPI left and MPI right (p<0.001).

Echocardiography findings' correlation with NT-proBNP, with leptin, TNF-α, IL-6 and with ferritin in participants and patients as shown in table 4. It was observed that NT-pro BNP, leptin, TNF-α, Interleukin and ferritin were not correlated to each other except TNF-α and IL-6 (p=0.001) but in participants the pattern was different. It also revealed that left DT was correlated with IL_6(p=0.028) and ferritin (p=0.013). Left Peak A with IL-6 (p=0.028) and ferritin (p=0.001). Right a was correlated with IL_6 (p=0.004) and ferritin (p=0.045). Right AT was correlated with NT-Pro BNP (p=0.008) and TNF-α (p=0.035). Right DT was correlated with NT-Pro BNP (p=0.018), Right peak E was correlated with TNF-α (p=0.013) and IL-6 (p=0.022). Right peak A with ferritin (p=0.017). Right ET and Left ET were correlated with all the markers in the study except leptin. IVSD was correlated with NT -Pro BNP (p=0.015). Leptin (p=0.020) and ferritin (p=0.011). LVDD was correlated with NT- pro BNP (p<0.001) and Ferritin (p=0.011). PWD was correlated with NT-Pro BNP, IL-6 and Ferritin significantly. IVSS and LVDS were significantly correlated just with Ferritin and TNF_α respectively. Both EF and FS were correlated with NT-pro BNP, TNF-α ,IL-6 and Ferritin significantly. Regarding to the table, approximately, all heart findings were correlated with IL-6, most of the heart findings were correlated with ferritin and NT-pro BNP and some of heart findings were correlated with TNF-α and Leptin. The table also revealed that right AT(p=0.011), right DT (p=0.022). IVSD (p=0.002), LVDD (p=0.001), PWD (p=0.031), EF (p<0.001), FS(p<0.001), LVMI (p<0.001), Simpson LVSD(p<0.001), Simpson EF (p=0.013), QT(p=0.032), BMI (p<0.001) were correlated with NT-Pro BNP significantly. Among the findings in the study, QTc (p=0.009) and Qtcd (p=0.002) were correlated with leptin significantly. Heart finding of Left MPI (p=0.034) was correlated with TNF-α and Simpson LVSD (p=0.037) was correlated with IL-6 significantly. Echocardiography findings in the study of ET(p=0.002), right peak A(p=0.034), PWD (p=0.048) and IVSS (p=0.001) were correlated with ferritin significantly.

Table 1: Gender Distribution in Case and Controls (n=228)

Gender	Statistics	Participants		Total	X^2	P value
		Control	Case			
Females	n (%)	49(48.5%)	52(51.5%)	101	0.271	0.602
Males	n (%)	65(52.0%)	60(48.0%)	125		
Total	n (%)	114(50.4%)	112(49.6%)	226		
Participants		n	Mean	SD	t value	p value
Age	Control	114	15.43	6.771	-1.418	0.158
	Case	114	16.77	7.403		

Table 2: Case-Control Comparison in Major Variables (n=228)

Variables	Groups	Mean	SD	Mean Rank	Sum of Ranks	M-W U	P value
NT-proBNP	Control	93.11	164.56	79.69	9084.50	2529.50	<0.001
	Case	439.79	817.57	147.92	16566.50		
Leptin	Control	6.58	9.98	115.86	13208.00	6115.00	0.584
	Case	4.20	5.90	111.10	12443.00		
TNF- α	Control	24.06	13.43	86.92	9909.00	3354.00	<0.001
	Case	40.37	19.21	140.55	15742.00		
Interleukin 6	Control	2.97	1.02	58.31	6647.00	92.00	<0.001
	Case	25.88	15.08	169.68	19004.00		
Height	Control	159.32	13.76	142.55	16251.00	3072.00	<0.001
	Case	142.29	19.31	83.93	9400.00		
Weight	Control	49.05	12.94	141.32	16110.50	3212.50	<0.001
	Case	36.09	13.03	85.18	9540.50		
Iron	Control	85.23	26.64	57.51	6556.00	1.00	<0.001
	Case	272.37	50.09	170.49	19095.00		
Ferritin	Control	52.37	24.34	57.50	6555.00	0.00	<0.001
	Case	4830.44	3989.58	170.50	19096.00		

Table 3: Echocardiography Findings' Comparison between Case and Controls (n=228)

Variables	Groups	Mean	SD	Mean Rank	Sum of Ranks	M-W u	P Value
Left a	Control	419.84	38.36	103.25	11770.5	5215.5	0.017
	Case	427.49	44.95	123.93	13880.5		
Left AT	Control	59.74	6.87	109	12425.5	5870.5	0.284
	Case	61.15	8.77	118.08	13225.5		
Left DT	Control	133.85	21.85	102.04	11632	5077	0.008
	Case	143.38	26.76	125.17	14019		
peak E Left	Control	98.52	20.68	116.62	13295	6028	0.469
	Case	96.47	17.38	110.32	12356		
Peak A Left	Control	49.57	9.57	102.97	11738.5	5183.5	0.015
	Case	54.59	13.98	124.22	13912.5		
Right a	Control	432.14	36.54	98.23	11198	4643	0.001
	Case	451.94	44.83	129.04	14453		
Right AT	Control	64.18	9.66	109.11	12438	5883	0.302
	Case	66.09	11.56	117.97	13213		
Right DT	Control	136.04	24.39	109.04	12430.5	5875.5	0.299
	Case	139.78	24.73	118.04	13220.5		
Right peak E	Control	69.19	12.2	122.77	13995.5	5327.5	0.032
	Case	64.41	19.33	104.07	11655.5		
Peak A Right	Control	48.35	12.12	104.99	11968.5	5413.5	0.048
	Case	50.03	15.74	122.17	13682.5		
Right ET	Control	293.22	29.26	145.97	16641	2682	0.001
	Case	264.38	23.11	80.45	9010		
Aod	Control	2.24	0.42	112.94	12875.5	6320.5	0.897
	Case	3.04	4.32	114.07	12775.5		
LAd	Control	2.37	0.45	93.11	10614	4059	0.001
	Case	3.62	5.08	134.26	15037		
Aos	Control	2.13	0.4	118.14	13467.5	5627.5	0.185
	Case	2.75	3.82	106.66	11732.5		
LAs	Control	1.56	0.3	89.07	10154	3599	0.001
	Case	2.51	3.67	136.78	15046		
Left ET	Control	293.95	23.02	162.37	18510	813	0.001
	Case	246.31	22.12	63.76	7141		
IVSD	Control	0.72	0.14	101.29	11546.5	4991.5	0.004
	Case	0.77	0.13	125.93	14104.5		
LVDD	Control	4.11	0.5	103.78	11831	5276	0.024
	Case	4.26	0.76	123.39	13820		
PWD	Control	0.38	0.07	106.71	12164.5	5609.5	0.113
	Case	0.4	0.08	120.42	13486.5		
IVSS	Control	0.9	0.18	106.49	12139.5	5584.5	0.103
	Case	0.95	0.18	120.64	13511.5		
LVDS	Control	2.21	0.33	97.23	11084.5	4529.5	0.001
	Case	3.26	4.29	130.06	14566.5		

Variables	Groups	Mean	SD	Mean Rank	Sum of Ranks	M-W u	P value
PWS	Control	0.38	0.06	103.34	11780.5	5225.5	0.018
	Case	0.52	0.62	123.84	13870.5		
EF	Control	75.36	14.91	149.04	16991	2332	0.001
	Case	53.22	31.09	77.32	8660		
FS	Control	43.82	11.87	150.54	17162	2161	0.001
	Case	29.41	17.63	75.79	8489		
Simpson LVDD	Control	72.54	31.49	109.98	12538	5983	0.414
	Case	85.77	102.66	117.08	13113		
Simpson LVSD	Control	36.75	17.63	103.28	11773.5	5218.5	0.018
	Case	43.61	21.37	123.91	13877.5		
Simpson EF	Control	49.32	9.84	127.18	14498	4825	0.001
	Case	44.21	10.17	99.58	11153		
QT	Control	0.35	0.02	81.46	9286	2731	0.001
	Case	0.37	0.03	146.12	16365		
QTc	Control	0.44	0.04	92.81	10580	4025	0.001
	Case	0.48	0.06	134.56	15071		
NFQTc	Control	0.43	0.04	99.74	11370	4815	0.001
	Case	0.44	0.03	127.51	14281		
QTd	Control	40.75	6.63	117.91	13441.5	5881.5	0.139
	Case	40.18	4.4	109.01	12209.5		
QTcd	Control	50.35	9.53	108.37	12354.5	5799.5	0.233
	Case	51.37	8.77	118.72	13296.5		
NFQTcd	Control	48.78	9.2	127.07	14486	4837	0.002
	Case	46.76	6.77	99.69	11165		
R in V_5	Control	8.37	2.84	113.63	12954	6369	0.975
	Case	8.52	2.5	113.37	12697		
S in V_1	Control	4.7	2.31	105.43	12018.5	5463.5	0.059
	Case	5.45	2.83	121.72	13632.5		
H R	Control	98.97	20.33	131.3	14968	4355	0.001
	Case	88.86	21.63	95.38	10683		
Left Peak E /A	Control	2.02	0.46	128.66	14667.5	4655.5	0.001
	Case	1.85	0.46	98.07	10983.5		
Right Peak	Control	1.48	0.31	127.24	14505	4818	0.001
E/A	Case	1.34	0.34	99.52	11146		
BMI	Control	19.02	3.23	131.91	15038	4285	0.001
	Case	17.07	2.67	94.76	10613		
RWT	Control	0.19	0.02	112.78	12856.5	6301.5	0.867
	Case	0.2	0.12	114.24	12794.5		
LA/AO in Diastole	Control	1.08	0.19	92.32	10524.5	3969.5	0.001
	Case	1.21	0.19	135.06	15126.5		
LA/AO in Systole	Control	0.75	0.15	83.26	9491.5	2936.5	0.001
	Case	0.92	0.19	142.8	15708.5		
LVMI(g/m^2)	Control	29.43	11.76	101.33	11552	4997	0.005
	Case	33.8	12.59	125.88	14099		
MPI Left	Control	0.44	0.16	67.77	7726	1171	0.001
	Case	0.74	0.19	160.04	17925		
Right MPI	Control	0.48	0.15	73.58	8388	1833	0.001
	Case	0.71	0.16	154.13	17263		

Table 4: The Echocardiography Findings' Correlation with NT-pro BNP, Leptin, TNF_α , Interleukin and Ferritin in Patients and Participants (n=228)

		Patients					Participants				
Variables		**NT-pro BNP**	**Leptin**	**TNF-α**	**IL-6**	**Ferritin**	**NT-pro BNP**	**Leptin**	**TNF-α**	**IL-6**	**Ferritin**
NT-pro BNP	Pearson correlation		-0.128	-0.004	0.01	-0.085		-0.117	0.128	0.221	0.12
	P value		0.180	0.967	0.85	0.371		0.079	0.055	0.001	0.06
leptin	Pearson correlation			-0.041	0.13	-0.052			-0.101	-0.062	-0.11
	P value			0.669	0.16	0.589			0.129	0.353	0.08
TNF_α	Pearson correlation				0.30	0.085				0.475	0.33
	P value				0.00	0.374				0.000	0.00
IL_6	Pearson correlation					0.043					0.49
	P value					0.652					0.001
Left a	Pearson correlation	-0.087	0.038	-0.149	-0.02	-0.081	-0.043	0.003	-0.065	0.056	0.01
	P value	0.362	0.689	0.118	0.78	0.397	0.521	0.960	0.327	0.401	0.84
Left AT	Pearson correlation	-0.147	-0.013	-0.028	-0.06	0.037	-0.091	0.030	0.054	0.031	0.08
	P value	0.121	0.888	0.770	0.48	0.700	0.174	0.659	0.423	0.641	0.22
Left DT	Pearson correlation	-0.183	0.105	-0.026	0.00	0.070	-0.086	0.040	0.090	0.146	0.16
	P value	0.054	0.269	0.783	0.93	0.466	0.197	0.553	0.178	0.028	0.01
Left peak E	Pearson correlation	0.045	0.000	0.003	-0.06	0.114	-0.014	0.064	-0.020	-0.069	0.02
	P value	0.639	0.998	0.973	0.52	0.233	0.835	0.342	0.760	0.304	0.75
Left Peak A	Pearson correlation	-0.037	0.059	0.005	-0.00	0.124	0.029	0.047	0.078	0.147	0.21
	P value	0.702	0.536	0.957	0.96	0.193	0.667	0.486	0.244	0.028	0.00
Right a	Pearson correlation	-0.119	0.072	-0.064	0.02	-0.035	-0.027	-0.030	0.033	0.190	0.13
	P value	0.212	0.450	0.505	0.81	.713	0.692	0.652	0.626	0.004	0.04
Right AT	Pearson correlation	-0.240	0.081	0.143	0.09	0.038	-0.177	-0.043	0.140	0.117	0.08
	P value	0.011	0.398	0.133	0.31	0.691	0.008	0.520	0.035	0.080	0.22
Right DT	Pearson correlation	-0.217	0.025	0.022	-0.04	0.008	-0.157	-0.009	0.075	0.035	0.05
	P value	0.022	0.791	0.816	0.67	0.933	0.018	0.895	0.260	0.601	0.42

Variables		Patients					Participants				
		NT-pro BNP	Leptin	TNF-α	IL-6	Ferritin	NT-pro BNP	Leptin	TNF-α	IL-6	Ferritin
Right peak E	Pearson correlation	-0.038	0.021	-0.117	-0.07	0.294	-0.090	0.005	-0.166	-0.153	0.09
	P value	0.694	0.830	0.220	0.41	0.002	0.180	0.942	0.013	0.022	0.17
Right peak A	Pearson correlation	-0.065	0.167	-0.062	-0.10	0.200	-0.037	0.092	-0.037	-0.009	0.15
	P value	0.494	0.078	0.514	0.29	0.034	0.582	0.170	0.580	0.888	0.01
Right ET	Pearson correlation	-0.121	-0.024	-0.041	-0.03	0.099	-0.216	-0.059	-0.205	-0.366	-0.27
	P value	0.204	0.805	0.669	0.75	0.298	0.001	0.376	0.002	0.000	0.00
Aod	Pearson correlation	-0.066	-0.053	0.065	-0.03	0.018	-0.030	-0.056	0.106	0.071	0.09
	P value	0.486	0.581	0.497	0.69	0.849	0.654	0.399	0.113	0.287	0.13
LAd	Pearson correlation	-0.065	-0.065	0.056	-0.03	-0.003	-0.015	-0.065	0.117	0.101	0.11
	P value	0.495	0.498	0.558	0.69	0.979	0.822	0.327	0.079	0.130	0.09
Aos	Pearson correlation	-0.071	-0.059	0.070	-0.04	0.023	-0.039	-0.058	0.102	0.056	0.09
	P value	0.460	0.537	0.468	0.66	0.812	0.561	0.386	0.128	0.402	0.17
LAs	Pearson correlation	-0.055	-0.078	0.057	-0.03	0.002	0.000	-0.071	0.116	0.114	0.11
	P value	0.569	0.420	0.555	0.75	0.983	1.000	0.291	0.083	0.090	0.07
Left ET	Pearson correlation	0.000	0.046	0.071	0.09	0.007	-0.214	0.030	-0.264	-0.507	-0.47
	P value	0.998	0.632	0.455	0.33	0.939	0.001	0.652	0.000	0.000	0.00
IVSD	Pearson correlation	-0.296	-0.034	-0.053	-0.03	0.089	-0.161	-0.155	0.082	0.119	0.16
	P value	0.002	0.720	0.576	0.69	0.353	0.015	0.020	0.217	0.073	0.01
LVDD	Pearson correlation	-0.317	0.065	-0.001	0.00	0.144	-0.238	-0.079	0.061	0.091	0.16
	P value	0.001	0.499	0.994	0.92	0.129	0.000	0.234	0.363	0.173	0.01
PWD	Pearson correlation	-0.204	0.019	0.049	0.17	0.187	-0.135	-0.095	0.098	0.182	0.19
	P value	0.031	0.838	0.606	0.06	0.048	0.043	0.155	0.140	0.006	0.00
IVSS	Pearson correlation	-0.152	-0.017	-0.037	0.05	0.322	-0.092	-0.108	0.042	0.114	0.24

Variables		Patients					Participants				
		NT-pro BNP	Leptin	TNF-α	IL-6	Ferritin	NT-pro BNP	Leptin	TNF-α	IL-6	Ferritin
	P value	0.110	0.855	0.701	0.58	0.001	0.167	0.105	0.531	0.088	0.00
LVDS	Pearson correlation	-0.075	-0.055	0.080	-0.02	0.015	-0.023	-0.059	0.135	0.106	0.12
	P value	0.432	0.566	0.403	0.76	0.872	0.730	0.380	0.043	0.111	0.06
PWS	Pearson correlation	-0.055	-0.055	0.072	-0.01	0.037	-0.011	-0.063	0.124	0.108	0.13
	P value	0.563	0.565	0.447	0.91	0.695	0.872	0.343	0.063	0.106	0.05
EF	Pearson correlation	-0.627	0.144	-0.021	0.05	0.087	-0.611	0.127	-0.165	-0.276	-0.21
	P value	0.000	0.129	0.825	0.58	0.364	0.000	0.056	0.013	0.000	0.00
FS	Pearson correlation	-0.607	0.129	-0.004	0.06	0.083	-0.558	0.036	-0.176	-0.289	-0.23
	P value	0.000	0.177	0.969	0.52	0.387	0.000	0.589	0.008	0.000	0.00
Sim LVDD	Pearson correlation	-0.168	-0.002	-0.084	0.17	0.091	-0.143	-0.050	-0.023	0.178	0.12
	P value	0.076	0.981	0.376	0.06	0.341	0.031	0.456	0.736	0.007	0.06
Sim LVDS	Pearson correlation	-0.399	0.119	0.079	0.19	0.117	-0.270	-0.069	0.129	0.226	0.18
	P value	0.000	0.210	0.406	0.03	0.219	0.000	0.301	0.052	0.001	0.00
Sim EF	Pearson correlation	0.235	-0.167	-0.012	-0.09	-0.078	0.090	0.045	-0.133	-0.226	-0.20
	P value	0.013	0.078	0.904	0.31	0.414	0.177	0.497	0.047	0.001	0.00
QT	Pearson correlation	-0.202	0.004	0.018	0.03	0.168	-0.003	-0.071	0.189	0.343	0.38
	P value	0.032	0.964	0.852	0.73	0.076	0.961	0.291	0.004	0.000	0.00
QTc	Pearson correlation	-0.176	0.247	0.088	0.09	0.091	-0.025	0.006	0.156	0.281	0.25
	P value	0.064	0.009	0.358	0.30	0.339	0.713	0.934	0.019	0.000	0.00
NFQTc	Pearson correlation	-0.006	0.039	0.112	0.07	0.082	0.042	-0.032	0.083	0.125	0.12
	P value	0.952	0.684	0.238	0.44	0.388	0.534	0.636	0.212	0.061	0.06
QTd	Pearson correlation	-0.008	0.150	-0.042	-0.02	0.014	0.014	0.086	0.019	-0.044	-0.02
	P value	0.932	0.115	0.657	0.82	0.887	0.838	0.198	0.779	0.512	0.69
QTcd	Pearson correlation	0.002	0.283	0.042	0.02	0.024	0.056	0.063	0.067	0.054	0.04
	P value	0.983	0.002	0.658	0.79	0.798	0.401	0.345	0.319	0.421	0.45

NFQTcd	Pearson correlation	0.137	0.173	-0.041	-0.03	-0.024	0.073	0.049	-0.038	-0.103	-0.09
	P value	0.150	0.069	0.671	0.74	0.799	0.274	0.465	0.566	0.123	0.17
R in V_5	Pearson correlation	-0.035	-0.095	0.034	-0.12	0.105	-0.001	0.028	0.013	-0.031	0.07
	P value	0.712	0.320	0.718	0.19	0.271	0.985	0.672	0.843	0.638	0.28
S in V_1	Pearson correlation	-0.003	0.145	-0.091	0.04	-0.061	0.013	0.033	-0.003	0.135	0.05
	P value	0.974	0.128	0.339	0.64	0.520	0.851	0.625	0.969	0.043	0.38
HR	Pearson correlation	0.078	0.092	0.081	-0.02	0.048	-0.016	0.011	-0.075	-0.184	-0.12
	P value	0.411	0.336	0.396	0.76	0.612	0.808	0.865	0.261	0.006	0.05
Left Peak E / A	Pearson correlation	0.032	-0.063	-0.006	-0.05	-0.068	-0.051	-0.019	-0.081	-0.163	-0.16
	P value	0.735	0.508	0.952	0.60	0.473	0.450	0.782	0.226	0.014	0.01
Right Peak E / A	Pearson correlation	0.022	-0.171	0.090	0.06	0.071	-0.059	-0.084	-0.125	-0.125	-0.10
	P value	0.821	0.071	0.344	0.47	0.459	0.375	0.211	0.061	0.062	0.13
RWT	Pearson correlation	0.015	-0.070	0.104	0.11	-0.060	0.035	-0.046	0.114	0.137	0.01
	P value	0.874	0.465	0.276	0.22	0.530	0.601	0.495	0.088	0.040	0.87
LA/Ao in Diastole	Pearson correlation	0.047	-0.108	-0.086	-0.03	0.050	0.132	-0.069	0.107	0.230	0.24
	P value	0.620	0.258	0.368	0.67	0.600	0.047	0.302	0.108	0.000	0.00
LA/Ao in Systole	Pearson correlation	0.140	-0.157	-0.032	0.03	-0.054	0.236	-0.105	0.148	0.350	0.26
	P value	0.144	0.102	0.742	0.72	0.575	0.000	0.118	0.026	0.000	0.00
LVM	Pearson correlation	-0.381	-0.007	-0.002	0.04	0.175	-0.236	-0.147	0.096	0.151	0.21
	P value	0.000	0.938	0.985	0.61	0.065	0.000	0.028	0.151	0.023	0.00
LVMI (g/m2)	Pearson correlation	-0.381	-0.007	-0.002	0.04	0.175	-0.236	-0.147	0.096	0.151	0.21
	P value	0.000	0.938	0.985	0.61	0.065	0.000	0.028	0.151	0.023	0.00
Left MPI	Pearson correlation	-0.090	-0.004	-0.200	-0.09	-0.079	0.139	-0.033	0.169	0.453	0.39
	P value	0.344	0.970	0.034	0.33	0.407	0.036	0.618	0.011	0.000	0.00
Right MPI	Pearson correlation	-0.004	0.111	-0.028	0.06	-0.128	0.175	0.022	0.208	0.471	0.33
	P value	0.969	0.243	0.773	0.50	0.178	0.008	0.745	0.002	0.000	0.00
BMI	Pearson correlation	-0.403	0.016	0.111	0.06	0.109	-0.306	0.006	-0.075	-0.205	-0.15
	P value	0.000	0.867	0.245	0.51	0.251	0.000	0.929	0.263	0.002	0.02

DISCUSSION

From the study resulted that NT-pro BNP, TNF-α, IL-6 and ferritin were higher in case and leptin was same in groups. Echocardiography findings' of ATt, DTT, right peak E, IVSD, LVDD, PWD, EF, FS, LVMI, Simpson LVSD, Simpson EF, QT, BMI were correlated with NT-Pro BNP. QTc and QTcdwere correlated with leptin. Heart valueof left MPI was correlated with TNF_α and Simpson LVSD was correlated with interleukin-6. ET, peak At, PWD and IVSS) were correlated with ferritin. The results of the present study revealed that NT-pro BNP, TNF-α, IL-6, ferritin were higher in case but, leptin had similar means in case and controls.

Khalilian et al., Ashenaet al., Aessoposet al., found that ferritin serum level was lower in control compared to patients in which was lower than the level measured in the present study in the patients it could be resulted from the less frequent blood transfusions and misusing of iron-chelation therapy[6,11,13]. Shivanna et al., conducted a study on thalassemia patients and found that the majority of echocardiography findings were correlated with ferritin. Ibrahim et al., conducted a study on pediatric thalassemia compared with control and concluded, ferritin was significantly varied between groups[17,18].

In the present study serum leptin levels were similar in thalassemia patients and controls. Shaharamian et al., concluded that thalassemia patients had lower leptin level and higher ferritin level compared to controls[19]. Choobine et al., resulted that the serum leptin level in patients was higher than the present study. Al-Naama et al., presented that, leptin meaningful was lower in thalassemia patients and ferritin was higher[20,21]. Many studies implicated to this fact that NT-pro BNP is a sensitive bio marker to detect asymptomatic LV dysfunction especially with an important role in diagnostic and prognostic thalassemia implications and proposed an increase of NT-pro BNP in thalassemia patients compared to controls.[1,22,23]

Abo-Shanabresulted that IL-6 was different in thalassemia patients compared to healthy ones. The results showed that the level of interleukin were significantly higher in patients with cardiac involvements.[23] The present study showed a low level of IL-6 for the asymptomatic patients compared to the Elzubeir study that conducted a survey on Sudanese patients and found that the severity of disease was correlated directly with the level of IL-6. Serum level of IL-6 had higher level in Patients' compared to healthy individuals similar with the present study result. Abnormal IL-6 production may play a significant role in a number of diseases, such as autoimmune diseases, chronic inflammation, and lymphoid malignancies, which may be associated with certain viruses.[24] A broad range of cytokines such as, granulocyte-macrophage-colony-stimulating factor (GM-CSF), IL-1, IL-3, IL-6, IL-8 and TNF-α are released by activated endothelium and these have been detected in the plasma of patients with SCD.[25] To confirm more ,other research found that thalassemia patients have higher serum levels of mediators of inflammation, such as IL-6, IL-18, IL-1, and TNF-α compared to healthy people.[26] Therefore, it was hypothesized that a relationship between serum chemokines and inflammatory responses in thalassemia patients may be established because of the presence of active inflammation in these patients.[27]

It was suggested that an increase in TNF-α could be a cause for macrophage activation due to iron overload and the antigenic stimulation induced by chronic transfusion therapy. The activated macrophages were selectively phagocytosing apoptotic erythroid precursors, thereby contributing to ineffective erythropoiesis.[28] Garadah et al., reported that TNF-α had higher level in patients compared to controls.Laurentino et al. resulted that the serum levels of TNF-α were significantly higher in SCA patients compared to healthy individuals similar to Lanaro et al., with the same target.[29,30,31] Ragab et al.,reported higher median values for the serum TNF-α for thalassemia major compared to talassemia intermediate and controls and also resulted that both thalassemia major and intermediate patients had higher level of TNF-α compared to controls. Noori et al., conducted some studies with the aims of echocardiography findings comparison between thalassemia patients and healthy group.[1,16,32] In all studies, Noori concluded that left heart findings of EF, FS and MPI were varied in groups in which were similar with the present study. EF and FS were higher and MPI was lower in controls compared to patients in all Noori et al., studies similar to the present study. The result of the LVMI was lowering in control similar with the present study.[16] LVDD was lower and higher in control when in the present study, it was higher in control.[1,16] Right ejection time was lower in case resulted by Noori et al., similar with the present but in the another study they found similarity inpatients andcontrol.[1,16,32] LAd/Aod and LAs/Aos were lower in controls in the study conducted by Nooriet al., and the results were similar with the present study.[1] Nooriet al., presented that MPI and Peak E/A were different between case and control in the right heart that all were similar with the present study.[16,1,32] However, Bosi et al., found a weak but significant correlation between left ventricular ejection fraction and serum ferritin concentration, where patients with a high ferritin concentration (>2500 ng/ml) had a lower ejection fraction than patients with a low level.[33] In our study found that EF and FS were dissimilar but Simpson EF was similar with Bosiet al.,.[33] Borgna-Pignattiet al., and Khalilianet al., demonstrated that the serum ferritin <2500 ng/ml was safe in patients with thalassemia major observed a negative correlation between serum ferritin and left ventricular ejection fraction but Derchi et al., reported that this data highlighted the importance of careful evaluation of cardiac functional status in patients.[11,34,35] Heart diseases are the base case for prognosis and estimating the survival in major thalassemia patients, in this regards, myocardia iron deposition seems to be a major development trigger cardiac involvements in these patients.[1] Khalilian et al.,evaluatedthe relationship between ferritin level and ejection fraction and found no significant relationship, when we found a significant correlation of PWD and IVSS in left heart, peak E and Peak A in right heart.[11] The difference between these two studies was likely due to the number of echocardiography findings and age of participants similar to the other report that didn't find any significant relationship of serum ferritin concentration with systolic and diastolic indices.[13] The likelihood reason that Ashena et al., khalilian et al., that could not found the relationship between echo findings and ferritin was that they studied a few number of echocardiography findings such as E/A and EF, in Khalilian et al, and only a few findings of left heart in Ashena et al. that in comparing with the present study were a few.[11,13] Ibrahim concluded that EF, FS were same in case and control dissimilar with the preset study findings.[17] But the functions of LVEDD, LVESD and LVM were more significantly in thalassemia patients compared to healthy group, when in our

study, all were similar except LVM. Aessopos et al. found high levels of NT-Pro BNP in patients with overt heart failure, independently of severity of cardiac insufficiency.[6,36] Sarray et al., conducted a study on sickle cell disease patients with vasoocclusive crisis and steady state condition to find the correlation between cytokine levels and VOC outcomes.[37] They observed that IL-6 was correlated with VOC duration and TNF-α was not correlated with any of VOC outcome. Since in these patients red blood cells have sickle form, they cause vasoocclusive in every organ such coronary heart vessel. In the present study, the correlation between echo findings and cytokines such as TNF-α and IL-6 evaluated and resulted that IL_6 had significant correlation with LVSD and TNF-α had significant correlation with left MPI in thalassemia patients. Noori et al., conducted a study to evaluate the correlation of NT-pro BNP and heart findings in in Beta Thalassemia patients and found that with using of a reference cut point for NT -Pro BNP, LAd, LVDS and RWT were correlated with NT-Pro BNP levels patients. The present study showed that right AT and DT, LVSD, LVDD, PWD, EF, FS, LVM were correlated with NT-pro BNP in thalassemia patients. In addition, two findings of ECG, QT and QTc also were correlated. Kim et al., lead a study of serum concentrations of Leptin correlation with myxomatous Mitral Valve Disease in animal's model and concluded no correlation between these two items. Fontes-Carvalho found that higher leptin levels were independently associated with diastolic dysfunctions as heart failure risks.[1,38,39] In the present study correlation analyzing showed that leptin levels were correlated with only ECG parameters of QTc and QTcd.

CONCLUSION

Results of the present study revealed that NT-pro BNP, TNF-α, IL-6, Ferritin were higher in cases but leptin had similar levels in cases and controls. Some of echocardio-graphy findings such as right AT, right DT, right peak E, IVSD, LVDD, PWD, EF, FS, LVMI, SIMPSON LVSD, SIMPSON EF, QT correlated with NT-Pro BNP. A few such as QTC and QTcd correlated with leptin. Heart finding of Left MPI correlated with TNF-α and Simpson LVSD correlated with IL-6. The findings of the study suggested that NT-pro BNP maybe the best biomarker for evaluation of cardiac functions in thalassemia patients

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