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Evaluation of Gluten-free Diet on the Heart Functions in Children with Celiac Disease

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Abstract

Background

Celiac disease (CD) is an autoimmune mediated gluten sensitive enteropathy and a chronic inflammatory condition caused by immune pathology in the small intestines in genetically susceptible individuals. This study aimed to determine the efficacy of gluten free diet on cardiac functions using conventional and Doppler tissue echocardiography (DTE) in children with CD compared to controls.

Materials and Methods

This case-control study was conducted on 107 children with CD and 45 healthy children. The study was performed in the Ali Ebne Abi Talib hospital, affiliated to Zahedan University of Medical Sciences, Zahedan (ZaUMS), Iran. After considering exclusion criteria, participants underwent echocardiography. Data were analyzed through SPSS software version 20.0.

***Results*:** Results showed that tTG-IgA was different in participants. Left MPI was different in control-positive ($p<0.001$), control-newly diagnosed ($p=0.024$), and positive-negative ($p<0.001$). Right MPI was different in control-positive ($p<0.001$), control-newly diagnosed ($p=0.024$), positive-negative ($p<0.001$), and negative-newly diagnosed ($p<0.001$). Left MPI' was different in control-positive ($p<0.001$), control-newly diagnosed ($p<0.001$), positive-negative ($p=0.014$), and negative-newly diagnosed ($p=0.010$). Right MPI' was different in control-positive ($p<0.001$), control-newly diagnosed ($p<0.001$), positive–negative ($p=0.010$), and negative-newly diagnosed ($p=0.034$). Left DT was different in positive-negative. Right ET was different in control-positive, control-newly diagnosed, positive-negative and negative-newly diagnosed. Right AT was different in positive-negative and positive-newly diagnosed.

Conclusion

It was concluded in patients with positive response to gluten free diet that some heart functions were similar to the controls and in patients with negative response, some were similar to newly diagnosed patients. Diastolic and systolic dysfunctions are important findings in CD children and TDE is a better method to identify cardiac involvements in subclinical patients with CD.

Key Words: Cardiac Involvements, Celiac, Children, Gluten.

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1- INTRODUCTION

Celiac disease (CD) is an autoimmune mediated gluten sensitive enteropathy and a chronic inflammatory condition caused by immune pathology in the small intestine in genetically susceptible individuals (1). It is a long term disease with a prevalence of 1- 2% in the European population and affects 0.6 to 1.0% around the world, with a wide difference in western countries (2). Prevalence has been reported 0.3% in Germany and 2.4% in Finland (3), and 18.41% in Sistan and Baluchestan province, Iran (4), and it is about 1.5 to 2 fold higher in females (2). CD is associated with the increasing risk of both lymphoma and mortality (2), which caused an increase in developing regions such as North Africa (5), and the Middle East due to strong changes in diet, wheat production and awareness of the disease (6).

It is also introduced as a systemic immune-mediated disorder which is caused by dietary gluten habits in genetically susceptible persons (2). Gluten is a protein found in wheat, barley and rye. These cereals are closely related grasses that contain prolamins or storage proteins that induce the autoimmune process in patients with celiac disease. About 95% of the rural and 85% of the urban population consume wheat and barley products in Iran, especially in the southeastern areas and it is shown that the prevalence of fluten sensitivity is similar to that of western countries (7). Moreover, the appearance of CD has changed throughout the years (1, 2, 5, 7). Rather than traditional side effects such as diarrhea, growth retardation, and abdominal pain and distention, atypical symptoms such as chronic constipation may be the only new signs of CD (8). CD is frequently associated with iron deficiency anemia, dermatitis herpetic form, thyroid disorders, diabetes mellitus, metabolic bone disease, peripheral neuropathy, endothelial dysfunction, infertility, and various connective tissue disorders (9). The frequency of CD is increased in patients with essential and optional cardiomyopathy (2, 8, 9). One of the common manifestations of CD is chronic malabsorption so that it may lead to secondary cardiomyopathy due to nutritional deficiencies. In CD, an intestinal abnormality caused myocardial damage through the immune-mediated mechanism that is probably due to an increase in the systemic absorption of various luminal antigens or infectious agents. Myocardial involvement can be secondary to an immune response directed against an antigen present in both the myocardium and small intestine. In chronic inflammatory diseases, connective tissue disorders and cardiac involvement are common. Thus, in CD, cardiac involvements are expected to have a role like that in other chronic inflammatory diseases. Another disorder frequently associated with CD is idiopathic dilated cardiomyopathy. Previous studies showed an immunologic associative mechanism and increased prevalence of CD in patients who have idiopathic dilated cardiomyopathy (2, 9, 10).

There is scarce data on the growing danger of cardiovascular occasions in patients with CD; for instance, in two population-based studies, an extended danger of atrial fibrillation (AF) has been accounted in patients with CD (11, 12). It is in a similar manner possible that cardiac rhythm disturbances such as AF might be related with the observed increment in the danger of stroke. The part of foundational irritation being developed from AF due to fibrotic changes in the chamber has been already settled (12). Doppler tissue echocardiography (DTE) assessment is a useful instrument to obtain affirmation of subclinical prevention of ventricular limit in the midst of clinical reliability in patients with CD (13). Akin et al., (14) performed a study on DTE and

conventional echocardiography to evaluate the impairment of myocardial diastolic functions in patients with CD. They concluded that DTE is more accurate and reliable. A small number of studies have identified the role of TDE in Coeliac disease (15). It has been widely accepted that Tissue Doppler echocardiography (TDE) is useful in analyzing subclinical ventricular functions in some cases such as valve regurgitation, anthracycline cardio toxicity, earlier phases of cardiomyopathies and heart transplant rejection (16,17). The present study hypothesized that identification and treatment of patients with CD before dilated cardiomyopathy and heart failure symptoms occur would play an important role in reducing cardiac morbidity and mortality of these patients. Therefore, we aimed to determine the cardiac involvement in children with CD and to evaluate the efficacy of gluten free diet on cardiac functions by using conventional and tissue Doppler echocardiography compared to controls.

2- MATERIALS AND METHODS

2-1. Study design and samples

This case-control study was performed on 107 patients with CD aged from 6 to 19 years and matched in sex and age with 45 controls selected from patients referred to the hospital for routine checkup. The study was performed in the Ali Ebne Abi Talib hospital affiliated to Zahedan University of Medical Sciences, Zahedan (ZaUMS), Iran from January 2016 to March 2018.

2-2. Criteria

Patients with obvious valvular heart disease, rhythm abnormality, structural, congenital heart disease, active infection, malignancy, other systemic inflammatory diseases, diabetes mellitus, renal insufficiency, chronic obstructive pulmonary disease and hypertension were excluded from the study. The same exclusion criteria were applied for the controls.

2-3. Measures and tools and methods

2-3-1. Celiac Measures

Eighty-five CD patients who were previously diagnosed and with regular gluten-free diet for at least 10 months were selected (11), and divided in two groups based on Tissue Transglutaminase-Immunoglobulin A (tTG-IgA) titer; participants with tTG-IgA > 20 were grouped as positive patients and the others were grouped as negative patients (2), and twenty-two newly diagnosed patients without any regimen were enrolled in the study. Three ml blood was taken from participants at 8:00 A.M. after overnight fasting. The samples were centrifuged and the separated sera were kept at -70 °C until measurement of tTG-IgA and total IgA. The samples were transferred to the biochemistry laboratory under cold chain conditions. Then, 250 microns of the isolated sera were used for serological tests using recombinant ELISA. It should be noted that the normal limit of tTG-IgA was 20 U/ml. Celiac disease was diagnosed based on a combination of clinical findings and laboratory tests of tTG-IgA with a cut point of 20.0 (13), and confirmation by intestinal biopsy.

2-3-2. Cardiac measurements

The whole study population underwent conventional echocardiography and Doppler tissue echocardiography by a cardiologist, using My Lab 60 instrument with 3-8-MHz transducers (made in Italy). The values of all necessary echocardiographic parameters, namely ejection fraction (EF), fractional shortening (FS), velocity of the blood flow through the heart valves, as well as the ejection time (ET), peak A velocity (A), peak E velocity (E), myocardial performance index (MPI), peak E (early mitral and tricuspid valve flow velocity) /

peak A (late mitral and tricuspid valve flow velocity) velocity (E/A ratio), Isovolumic relaxation time (IVRT), isovolumic contraction time (ICT) of both sides were measured with pulsed Doppler echocardiography (9). 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): 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): 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 (MPI/Tei Index) was calculated as a-b/b = (ICT + IRT)/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/m^2) = LVM / 2.7.

Doppler tissue echocardiography (DTE) was another method performed from the apical four-chamber width of the sample volume and was 3–5 mm for all sites interrogated (2,13). Myocardial velocity profiles of the lateral tricuspid annulus and lateral mitral annulus were obtained by placing the sample volume at the junction of the tricuspid annulus and the right ventricle (RV) free wall and at the junction of the mitral annulus and LV posterior wall, respectively. With this modality, the recorded values were the early (E) and late (A) diastolic mitral and tricuspid annular velocities, and the ratio of E/A. Right ventricle and left ventricle myocardial performance index (MPI) was obtained by dividing the sum of isovolumic relaxation time (IRT) and isovolumetric contraction time (ICT) by the ejection time (ET) (MPI = (ICT + IRT)/ET).

3- RESULTS

Normality test showed left a (p=0.200), left ejection time (p=0.062), left peak E velocity (p=0.092), right a(p=0.095), right peak E velocity (p=0.092), right peak E' velocity (p=0.200), right peak A velocity (p=0.200), right ET'(p=0.079), Left E/A (p=0.200), right E/E (p=0.200), left MPI (p=0.200), right MPI (p=0.200), left MPI(p=0.200), right MPI'(p=0.200). The remained variables had free distribution (**Table.1**) (*pleas see the table in the end of paper*). **Figure.1** showed that from 152 participants who took part in the study, 107 had CD, which was categorized with newly diagnosed (22), and those with gluten regime in two groups with positive (35) and negative (50) tTG-IgA.

The control groups consisted of 45 children. **Table.2** shows the comparison of normal variables and resulted that left ET was different in all paired groups except control-negative and negative–newly diagnosed. Right Peak E' velocity was not different in control-negative and positive-newly diagnosed (*pleas see the table in the end of paper*). Right ET' was not different in positive-negative, positive-newly diagnosed and negative-newly diagnosed. Left MPI was different in control-positive (p<0.001), control-newly diagnosed (p=0.024), and positive–negative (p<0.001). Right MPI was different in control-positive (p<0.001), control-newly diagnosed (p=0.024), positive–negative (p<0.001), and negative-newly diagnosed (p<0.001). Left MPI' was different in control-positive (p<0.001), control- newly diagnosed (p<0.001), positive –negative (p=0.014), and negative- newly diagnosed (p=0.010). Right MPI' was different in control-positive (p<0.001), control-newly diagnosed (p<0.001), positive–negative (p=0.010), and negative-newly diagnosed (p=0.034). **Table.3** shows the comparison

of free distributed variables of the study and resulted that tTG-IgA was different in all pairs of group (*pleas see the table in the end of paper*). Left deceleration time was different only in positive-negative (p=0.038). Right Ejection time was different in control-positive (p<0.001), control-newly diagnosed (p<0.001), positive-negative (p<0.001), and negative-newly diagnosed (p<0.001). Right acceleration time was different in positive-negative (p=0.004), and positive-newly diagnosed (p=0.007). Right deceleration time was different only in positive-negative (p=0.023). Left ET' was different in pair groups of control-negative (p=0.043), positive-negative (p<0.001), and positive-newly diagnosed (p=0.036). Left ICT' was different in pairs of control-new (p=0.001), and negative-newly diagnosed (p=0.027). Left IRT' was different in pairs of control-positive (p=0.015), control–negative (0.027), and control-newly diagnosed (p=0.003). Right ET' was different in pairs of control-positive (p<0.001), control-newly diagnosed (p<0.001), positive-negative (p<0.001), and negative-newly diagnosed (p=0.002). Controls had different values of right IRT' compared to newly diagnosed patients (p=0.027). Left A'/A was different in positive (p=0.021), and negative (p=0.028) patients compared to newly diagnosed patients when right A'/A had different values in newly diagnosed patients compared to controls (p=0.004) and positive-patients (p=0.008).

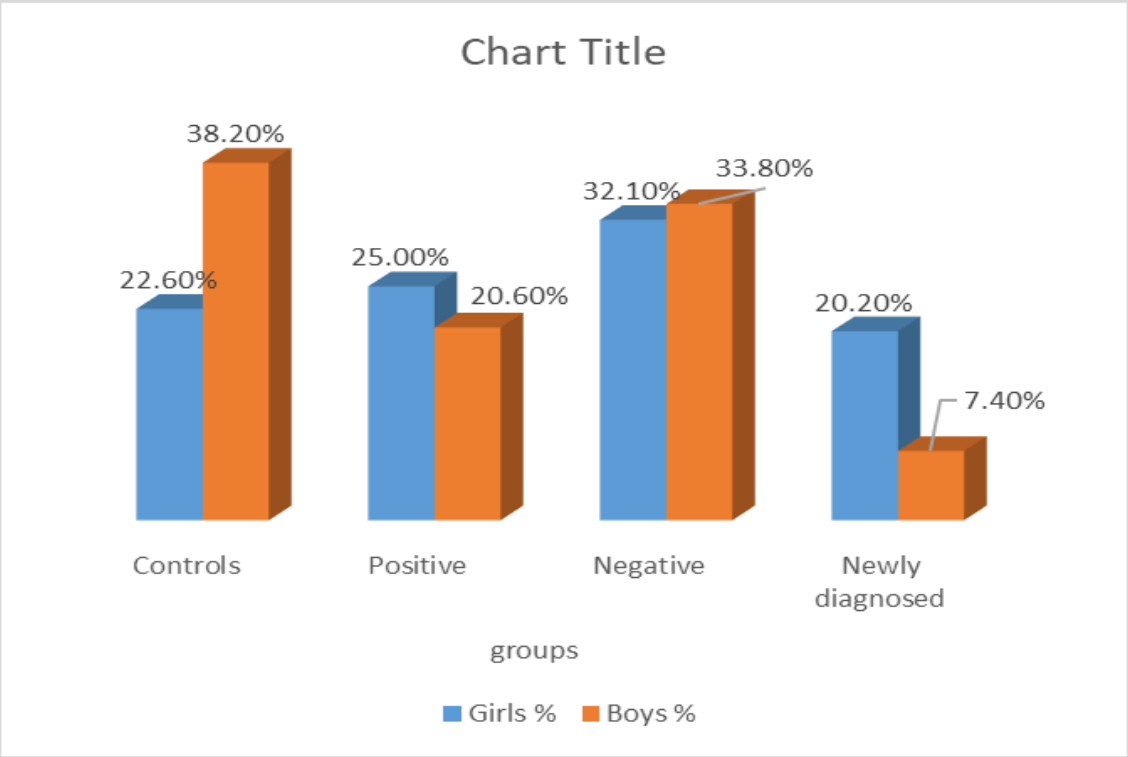

Fig.1: Sex frequency in groups of participants.

4- DISCUSSION

The study was performed to determine cardiac involvement in children with CD and to evaluate the efficacy of gluten free diet on cardiac functions. From the present investigation it was shown that left heart functions such as ET, MPI, MPI' and right heart functions such as peak E' velocity, ET', MPI, MPI' and ET' were different in case and controls. Comparing controls with patients whose response to free diet was negative, the right ET' was different. In comparing control with newly diagnosed patients, left ET, right peak E' velocity, right ET', and all MPI functions were different. The patients compared in the groups of positive and negative results showed that the variables of left ET, right peak E' velocity and all MPI functions were different. Left deceleration time was different in positive and negative patient groups. Right Ejection time was different in groups of control-positive, control-newly diagnosed, positive-negative and negative-newly diagnosed.

Right AT was different in the positive-negative and positive-newly diagnosed groups. Right DT was different only between positive and negative groups of patients. Left ET' was different in control and negative, positive and negative and positive and newly diagnosed groups. Left ICT' was different in control and new and negative and new. Left IRT' was different in control-positive, control-negative and control-newly diagnosed groups. Right ET' was different in control-positive, control-newly diagnosed, positive-negative and negative – newly diagnosed groups. Controls were different with newly diagnosed patients based on right IRT'. Newly diagnosed patients had different values of left A'/A compared to the other two groups of patients when right A'/A had different values compared to controls and positive groups. Diverse speculations have been advanced to clarify the reasons of cardiovascular contribution in CD. One hypothesis clarifies it with nourishing inadequacy activated by intestinal malabsorption, while another points to focuses on incendiary reaction in myocardial tissue caused by enactment of the invulnerable framework by expanded assimilation of various antigens following expanded intestinal penetrability (11). Various types of cardiac involvement have been described in CD, and cardiovascular diseases are the main causes of mortality in this group of patients (18). From the present study it is deduced that EF, left and right AT, left DT and right E/A ratio were not significant between case and control which was confirmed by Noori et al.'s study (10) that has been performed on CD in dilated cardiomyopathy. In this study, all functions were different between case and controls except EF, left AT, left DT, left atrium/aorta ratio, right AT, and right E/A velocity ratio.

In this regard, Sari et al. (19) utilized conventional echocardiography to evaluate cardiovascular findings in case and controls. They found functions such as: EF, left E, left A that were not significant, which is similar to the present study that found EF was not significant between patients and controls. Noori et al. (9, 13) directed two investigations on CD to evaluate cardiovascular associations by DTE and conventional echocardiography and obtained comparable results indicating that right ET had significant differences in the case and controls. Left MPI in conventional, ET, IRT and MPI by DTE had significant differences in the cases and controls. From their studies it was also revealed that left ET, left ICT, left IRT and left MPI by DTE had significant differences in case and controls. Akin et al. (14) assessed left ventricular functions by utilizing DTE and conventional techniques on patients with CD. They found that EF was not different in case and controls that confirmed the present results. They also found that left E ', and left E'/A' ratio were

significantly dissimilar to the present study. Fathy et al. (20) showed that left heart functions by DTI such as MPI, E', E'/A', E/E', ICT, IRT and ET were different in patients and controls. In this study, right MPI had the same trends. From the present study it can be concluded that right ET did not change in case compared to controls. Left MPI in conventional was significantly different between controls and patients (positive and newly diagnosed patients). Karpuz et al. (18), investigated preclinical atherosclerosis using aortic elasticity parameters in subclinical pediatric CD patients, and suggested that children with CD are at risk of early atherosclerosis, especially in group two. They also observed a significant decrease in left peak E velocity, left peak A velocity in the patients' groups.

The results in disagreement with the present study that concluded an increase in patient's groups. They also found an increase in left E/E' in patients comparable with the present study that presented decrease in positive and negative groups of patients with an increase in newly diagnosed patients. They also resulted that patients had significantly higher left ICT and left IRT values, and consequently higher left MPI values, in line with the present study. Peak E' velocity was lower and the mean of E/E' was higher in positive and negative groups of patients separately compared to controls. Present study showed that peak E' velocity and E/E' were higher in negative and newly diagnosed patients compared to other groups of participants and a similar trend was observed in controls and patients in Karpuz et al.'s study (18). Saylan et al. (15) conducted a study on subclinical cardiac dysfunction in children with CD in two groups' positive and negative serum endomysial antibody (EmA) compared with controls and concluded that EF and FS which are commonly used in the assessment of LV systolic function by conventional evaluation of transthoracic echocardiography (TTE), did not indicate significant difference between groups. There was no significant difference in Doppler echocardiography parameters including left E, left A, left E/A, and left E between patients' groups, while these parameters showed significant difference with controls. A significant difference was found between positive group and the controls in terms of left IRT and right ICT parameters. Left MPI showed a significant difference between patient groups and the controls, but not between patient groups. Saylan et al. (15) showed that left E', left A', right E', right MPI using TDE method were not significant between patient's groups, whereas there was a significant difference between patient groups and controls. Karpuz et al. (18) reported higher levels of right MPI in patients comparable with the results of the present study which demonstrated right MPI was increased in all patient groups except negative that was lower even than controls.

Right MPI was significantly higher in the positive group than the negative group and Peak A' velocity showed no significant difference in patients with CD compared to control group that is comparable with the present results. However, when cardiac functions were evaluated by TDI echocardiography, it was shown that both the left ventricle and the right ventricle had systolic and diastolic dysfunction in the patient group. Besides, Karpuz et al. (18) reported significant prolongation in the IRT and ICT at the mitral annulus and at the tricuspid annulus in children with CD. In the present study patients were divided in three groups and it was found that left ICT, left IRT were increased in patients when the right functions were similar in case and controls. Karpuz et al. (18), similarly, found a significant increase in left and right MPI by TDI in children with CD. Moreover, right MPI value was the

highest in the serum IgA-tTG antibody positive group. These results suggest that subclinical myocardial dysfunction may be present in both ventricles in patients with CD, and TDI can be used effectively in early detection of this disease. There is a well-known association between the presence of antibodies specific for celiac disease and the severity and prognosis of the disease. Furthermore, the higher right MPI in positive group suggests that cardiac involvement may be related to disease severity and diet compliance. Young adults with CD are under the risk of potentially increased atherosclerosis due to the underlying vascular and biochemical disorders (15); in this regard Saylan et al. (15), found significant difference in left ICT', right A', and right IRT' between patient groups and the controls and left IRT' and left MPI' had significant difference between two patient groups. Although left E, left A, left E/A, right E, and right E/A, which are used in the evaluation of diastolic functions by conventional DTE, showed a significant difference between patients and control group, no evidence of diastolic dysfunction was found in patients.

They also found a significant difference between patient groups in terms of left MPI as a marker of left ventricular dysfunction, with a higher left MPI value in positive patients. There was significant difference between patients and controls in terms of right E' and right MPI among right ventricular tissue Doppler echocardiographic parameters, whereas there is no significant difference between positive and negative patients. Karadaş et al. (11), performed a study on the subclinical effect of CD on the heart and the effect of gluten-free diet on cardiac functions. The study had three groups: patients newly diagnosed and who had not been on gluten-free diet, those who had been on regular gluten-free diet for at least 10 months and controls. They concluded that, left E/E' ratio was significantly lower in both CD patients groups. None of the patients had a left E/E′ ratio over 15. However, the average of this ratio was below 8 in the patients with CD, and it was significantly different than that of the controls. DT and IRT were significantly shorter in newly diagnosed compared to those who had been on regular gluten-free and the controls. Compared with the present study, prolonged IRT and left MPI measured with TDE may be a marker of early cardiac dysfunction. Considering all these data, to diagnose and treat childhood coeliac disease is important for the future of the patients. Regarding this importance, Saylan et al. (15) reported that in using both conventional echocardiography and TDE indices, significant differences were observed between CD patients and control group. Karadaş et al. (11) concluded that the TDE findings revealed that diastolic dysfunction is the earliest cardiac complication of pediatric CD; and Cevik et al. (15) reported that, the TDE parameters of LV myocardial performance index (MPI), and LV IVRT were effective in patients with CD. In line with the discussed data the present study determined the efficacy of TDE for the determination of the subclinical early stage of cardiac involvement in pediatric CD.

4-1. Limitation

Firstly, the sample size of our study was relatively small. Secondly, the cross-sectional design of the study prevented the ability to detect a direct causal relationship between the variables, such as the positive effect of gluten-free diet on cardiac function.

5- CONCLUSIONS

We found an association between timing of initial exposure to wheat, barley, and rye and the development of heart functions. Highlighted novelty concluded from the study is that in patients with positive response to gluten free diet, the

majority of heart functions were similar to the controls and in patients with negative response to gluten free diet, the majority of heart functions were similar to newly diagnosed patients. It was also concluded that diastolic and systolic dysfunction were important early findings in the children with CD and tissue Doppler echocardiography was a better method to identify subclinical early stage of cardiac involvement in patients with CD. Therefore, monitoring these parameters during the follow up may help to show the effectiveness of treatment in children with CD.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENTS

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8- AUTHORS CONTRIBUTION

Noor mohammad Noori supervised the study and controlled writing. Alireza Teimouri performed data analysis and wrote the manuscript. Touran Shahrahki took part in data collection and review.

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Table-1: Normality Test of Kolmogorov–Smirnov (K.S) on the study variables

Variables	Mean	SD	K.S	P value	Variables	Mean	SD	K.S	P- value
Age	8.94	3.777	0.104	<0.000	Right E'/E	0.221	0.0588	0.085	0.009
Left AT	60.86	9.306	0.12	<0.000	Right A'/A	0.26	0.957	0.449	<0.000
Left Peak A velocity	59.74	12.599	0.081	0.016	LVMI	15.8159	5.98671	0.108	<0.000
Right ET	279.3	42.134	0.108	<0.000	Right E/E'	4.87529	1.418916	0.11	<0.000
Right AT	63.69	11.236	0.167	<0.000	Left A/A'	8.4759	2.152602	0.091	0.004
Left DT	130.38	25.805	0.098	0.049	Right A/A'	6.03081	2.027885	0.135	<0.000
Right DT	125.2	23.391	0.093	0.003	Left A'/A	0.191	0.799	0.466	0.000
Right peak A velocity	51.707	12.0913	0.096	0.002	Left ET	253.34	29.878	0.07	0.062
FS	0.4268	0.05815	0.103	<0.000	Left a	410.645	42.8072	0.05	0.200
Left ET'	238.28	23.099	0.111	<0.000	Left peak E velocity	100.02	15.594	0.067	0.092
Left ICT'	68.282	13.0343	0.132	<0.000	Right peak E velocity	69.516	14.2247	0.067	0.092
Left IRT'	96.045	17.5327	0.113	<0.000	EF	0.7418	0.06737	0.066	0.200
Left peak E' velocity	15.989	13.4109	0.346	<0.000	Right Peak E' velocity	16.181	2.5445	0.059	0.200
Left peak A' velocity	7.295	1.6341	0.082	0.015	Right Peak A' velocity	9.063	2.2176	0.053	0.200
Right a	504.58	379.204	0.417	<0.000	Right ET'	245.13	19.503	0.068	0.079
Right ET'	233.35	58.437	0.236	<0.000	Left E/A	1.72741	0.36096	0.065	0.200
Right ICT'	69.016	13.576	0.096	0.002	Right E'/A'	1.7215	0.558048	0.094	0.002
Right IRT'	97.466	19.1491	0.099	0.001	Left E/E'	6.852	1.5995	0.058	0.200
LVM	42.75284	16.20567	0.107	<0.000	Left MPI	0.6383	0.219117	0.061	0.200
Right E/A	1.38358	0.30258	0.074	0.041	Right MPI	0.54642	0.241729	0.041	0.200
Left E'/A'	2.33409	2.597833	0.323	<0.000	Left MPI'	0.69177	0.106318	0.055	0.200
Left E'/E	0.165	0.1583	0.349	<0.000	Right MPI'	0.67704	0.123515	0.059	0.200

(') prim is an indicator to show that the measurements are based on DTE methods. SD: Standard deviation; Abbreviations: AT:Acceleration time, ET:ejection Time, DT: deceleration time. FS: Fractional shortening, IRT: isovolumic relaxation time, ICT: isovolumic contraction time, a: is the time interval between the end and the start of trans-mitral and trans-tricuspid flow, LVM: Left ventricular mass, E/A:peak E velocity / Peak A velocity (ratio) ; E / E':peak E velocity / Early diastolic myocardial, LVMI: Left ventricular mass index, EF: Ejection Fraction, MPI: myocardial performance index.

Table-2: The Results of parametric t- test for normally distributed variables in all groups

Variables	Groups	Mean	SD	*P-value	**P-value	***P-value	****P-value	*****P-value	*****P-value
Left a	Control	411.16	41.65	0.673	0.913	1.000	0.295	0.755	0.966
	Positive	400.29	43.37						
	Negative	416.92	43.38						
	Newly diagnosed	411.82	42.80						
Left ET	Control	269.33	25.17	<0.001	0.568	0.003	<0.001	0.002	0.052
	Positive	223.00	20.77						
	Negative	262.94	25.34						
	Newly diagnosed	247.05	23.49						
Left Peak E velocity	Control	99.38	13.47	1.000	0.992	0.312	0.998	0.315	0.196
	Positive	99.09	14.42						
	Negative	98.46	17.45						
	Newly diagnosed	106.36	16.45						
Right a	Control	432.93	50.62	0.276	0.947	0.813	0.472	0.916	0.945
	Positive	411.91	58.29						
	Negative	428.40	44.98						
	Newly diagnosed	421.05	57.03						
Right Peak E velocity	Control	70.24	15.12	0.927	0.979	0.997	0.994	0.893	0.952
	Positive	68.26	13.03						
	Negative	69.08	13.39						
	Newly diagnosed	71.02	16.62						
EF	Control	0.75	0.07	0.995	0.795	0.947	0.51	0.776	0.998
	Positive	0.75	0.06						
	Negative	0.73	0.07						
	Newly diagnosed	0.74	0.06						
Right Peak E' velocity	Control	16.95	2.42	0.001	1.000	0.004	0.001	1.000	0.003
	Positive	14.89	2.62						
	Negative	16.99	2.11						
	Newly diagnosed	14.83	2.30						
Right Peak A' velocity	Control	8.76	1.88	0.999	0.946	0.055	0.981	0.093	0.138
	Positive	8.82	2.29						
	Negative	9.00	2.34						
	Newly diagnosed	10.21	2.23						

Right ET’	Control	257.96	16.98	<0.000	<0.000	0.001	0.927	0.996	0.992
	Positive	238.37	19.16						
	Negative	240.78	17.16						
	Newly diagnosed	239.50	18.50						
Left E/A	Control	1.77	0.33	0.557	0.964	0.986	0.807	0.874	1.000
	Positive	1.66	0.43						
	Negative	1.73	0.36						
	Newly diagnosed	1.74	0.31						
Right E’/A’	Control	1.74	0.46	0.985	0.895	0.382	0.999	0.269	0.265
	Positive	1.78	0.51						
	Negative	1.76	0.72						
	Newly diagnosed	1.50	0.32						
Left E/E’	Control	6.88	1.51	0.995	0.959	0.882	0.996	0.803	0.658
	Positive	6.80	1.40						
	Negative	6.72	1.84						
	Newly diagnosed	7.19	1.56						
Left MPI	Control	0.53	0.17	<0.000	0.352	0.024	<0.000	0.146	0.382
	Positive	0.80	0.14						
	Negative	0.60	0.24						
	Newly diagnosed	0.68	0.23						
Right MPI	Control	0.45	0.25	<0.000	0.987	<0.000	<0.000	0.873	<0.000
	Positive	0.70	0.16						
	Negative	0.44	0.19						
	Newly diagnosed	0.74	0.20						
Left MPI’	Control	0.65	0.10	0.001	0.820	0.001	0.014	0.960	0.010
	Positive	0.74	0.10						
	Negative	0.67	0.11						
	Newly diagnosed	0.75	0.09						
Right MPI’	Control	0.62	0.11	<0.000	0.546	0.001	0.010	1.000	0.034
	Positive	0.74	0.11						
	Negative	0.66	0.13						
	Newly diagnosed	0.74	0.10						

(‘) prim noted to the DTE methods Abbreviations: a: is the time interval between the end and the start of trans-mitral and trans-tricuspid flow, ET:ejection Time, E/A:peak E velocity / Peak A velocity (ratio) ; E / E’:peak E velocity / Early diastolic myocardial, EF: Ejection Fraction, MPI: myocardial performance index. *p-value for control vs. positive; ** p-value for control vs. negative; *** p-value for control vs. new; **** p-value for positive vs. negative; ***** p-value for positive vs. new; *****p for positive vs. new.

Table-3: The Results of Non-parametric Mann-Whitney U Test for Non-Normally Distributed Variables in all Groups

Variables	Groups	Mean	SD	*P-value	**P-value	***P-value	****P-value	*****P-value	*****P-value
tTG-IgA	Control	7.73	1.80	<0.000	<0.000	<0.000	<0.000	<0.000	<0.000
	Positive	86.05	82.32						
	Negative	17.05	8.14						
	Newly diagnosed	147.50	85.54						
Left AT	Control	60.64	10.17	0.777	0.647	0.984	0.572	0.987	0.677
	Positive	59.97	6.99						
	Negative	61.58	9.06						
	Newly diagnosed	61.09	11.52						
Left DT	Control	132.13	29.38	0.255	0.4	0.909	0.038	0.402	0.429
	Positive	123.69	21.53						
	Negative	134.16	22.72						
	Newly diagnosed	128.82	30.11						
Left Peak A velocity	Control	57.73	11.24	0.154	0.829	0.151	0.209	0.85	0.175
	Positive	62.77	15.49						
	Negative	58.16	11.43						
	Newly diagnosed	62.61	12.04						
Right ET	Control	302.11	35.35	<0.000	0.97	<0.000	<0.000	0.774	<0.000
	Positive	242.83	28.74						
	Negative	300.42	31.94						
	Newly diagnosed	242.64	25.01						
Right AT	Control	62.64	11.03	0.184	0.112	0.118	0.004	0.007	0.672
	Positive	59.49	11.60						
	Negative	66.02	10.49						
	Newly diagnosed	67.23	10.98						
Right DT	Control	126.07	20.78	0.08	0.915	0.856	0.023	0.105	0.75
	Positive	117.63	25.59						
	Negative	128.50	23.79						
	Newly diagnosed	127.95	22.76						

Right Peak A velocity	Control	53.73	12.65	0.775	0.098	0.25	0.181	0.362	0.859
	Positive	52.97	11.29						
	Negative	49.52	11.90						
	Newly diagnosed	50.52	12.44						
FS	Control	0.43	0.06	0.745	0.413	0.232	0.236	0.2	0.893
	Positive	0.44	0.06						
	Negative	0.42	0.06						
	Newly diagnosed	0.42	0.05						
Left ET’	Control	236.60	24.14	0.092	0.043	0.649	<0.000	0.036	0.245
	Positive	227.31	20.77						
	Negative	246.98	21.40						
	Newly diagnosed	239.41	21.44						
Left ICT’	Control	64.42	10.52	0.081	0.22	0.001	0.562	0.109	0.027
	Positive	68.97	12.24						
	Negative	67.99	14.24						
	Newly diagnosed	75.76	13.52						
Left IRT’	Control	89.08	16.83	0.015	0.027	0.003	0.6	0.26	0.11
	Positive	98.49	16.69						
	Negative	97.18	17.57						
	Newly diagnosed	103.83	16.29						
Left Peak E’ velocity	Control	14.94	2.91	0.969	0.952	0.655	0.855	0.682	0.549
	Positive	14.96	2.64						
	Negative	18.06	23.09						
	Newly diagnosed	15.07	2.14						
Left Peak A’ velocity	Control	6.93	1.25	0.064	0.307	0.733	0.398	0.111	0.307
	Positive	7.78	1.89						
	Negative	7.39	1.59						
	Newly diagnosed	7.05	1.87						
Right ET’	Control	257.98	20.61	<0.000	0.751	<0.000	<0.000	0.104	0.002
	Positive	228.31	21.85						
	Negative	256.28	22.74						
	Newly diagnosed	236.22	19.98						

Right ICT’	Control	67.36	14.95	0.378	0.347	0.35	0.986	0.875	0.961
	Positive	69.02	12.52						
	Negative	70.29	14.76						
	Newly diagnosed	69.50	9.24						
Right IRT’	Control	93.20	16.73	0.187	0.417	0.027	0.619	0.324	0.174
	Positive	99.03	19.04						
	Negative	97.15	20.03						
	Newly diagnosed	104.44	20.80						
Right E/A	Control	1.34	0.28	0.801	0.124	0.227	0.068	0.198	0.847
	Positive	1.32	0.26						
	Negative	1.45	0.33						
	Newly diagnosed	1.44	0.33						
Left E’/A’	Control	2.23	0.62	0.113	0.395	0.769	0.294	0.077	0.369
	Positive	2.02	0.58						
	Negative	2.69	4.46						
	Newly diagnosed	2.25	0.56						
Left E’/ E	Control	0.15	0.04	0.85	0.69	0.603	0.758	0.583	0.299
	Positive	0.15	0.03						
	Negative	0.19	0.27						
	Newly diagnosed	0.14	0.03						
Right E’/E	Control	0.22	0.06	0.649	0.873	0.789	0.883	0.909	0.807
	Positive	0.23	0.06						
	Negative	0.22	0.05						
	Newly diagnosed	0.22	0.06						
Left A’/A	Control	0.12	0.03	0.5	0.351	0.108	0.911	0.021	0.028
	Positive	0.13	0.04						
	Negative	0.13	0.04						
	Newly diagnosed	0.12	0.04						
Right A’/A	Control	0.17	0.05	0.896	0.234	0.004	0.108	0.008	0.068
	Positive	0.17	0.05						
	Negative	0.19	0.06						
	Newly diagnosed	0.21	0.06						

LVMI	Control	16.59	6.99	0.142	0.964	0.709	0.105	0.403	0.678
	Positive	14.45	5.24						
	Negative	16.22	5.68						
	Newly diagnosed	15.63	5.66						
Right E/E’	Control	5.01	1.58	0.649	0.873	0.789	0.883	0.509	0.807
	Positive	4.73	1.27						
	Negative	4.82	1.27						
	Newly diagnosed	4.95	1.68						
Left A/A’	Control	8.59	2.19	0.500	0.351	0.126	0.911	0.021	0.028
	Positive	8.33	2.28						
	Negative	8.16	2.11						
	Newly diagnosed	9.21	1.89						
Right A/A’	Control	6.41	2.09	0.896	0.234	0.004	0.108	0.008	0.068
	Positive	6.34	2.02						
	Negative	5.87	2.09						
	Newly diagnosed	5.13	1.48						

(‘) prim noted to the DTE methods Abbreviations: AT:Acceleration time, ET:ejection Time, DT: deceleration time. FS: Fractional shortening, IRT: isovolumic relaxation time, ICT: isovolumic contraction time, E/A:peak E velocity / Peak A velocity (ratio) ; E / E’:peak E velocity / Early diastolic myocardial, LVMI: Left ventricular mass index. *p-value for control vs. positive; ** p-value for control vs. negative; *** p-value for control vs. new; **** p-value for positive vs. negative; ***** p-value for positive vs. new; *****p for positive vs. new.