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Cardiac Involvements in Patients with Celiac Disease by Doppler Tissue Echocardiography Compared to Conventional Echocardiography

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ABSTRACT

Background: Celiac disease (CD) is an autoimmune mediated gluten sensitive enteropathy and cardiac involvement in CD children is frequent.
Objectives: This study aimed to investigate cardiac involvements in patients with celiac disease by using Doppler Tissue Echocardiography and conventional echocardiography to identify myocardial dysfunctions in celiac patients compared to healthy individuals.
Patients and Methods: This case-control and approved study was performed on 120 children with celiac disease and 60 healthy children aged 1- 18 years old in a single center. Patients with valvular disease, rhythm abnormality, CHD, malignancy, systemic inflammatory diseases, diabetes mellitus, renal insufficiency, chronic obstructive pulmonary disease and hypertension were excluded from the study. The participants underwent echocardiography. Data were analyzed through SPSS 17 using Student's t-test and Mann-Whitney U. A P value of < 0.05 was considered as significant.
Results: Out of 120 patients with celiac, 55.83% were females and for the control group it was 43.33%. The participants in the case and control groups were matched for sex and age. Weight and height showed significant differences between the groups. Right ejection time had significant mean differences of 245.30 ± 24.60 and 253 ± 22.66 for the case and control groups respectively with the $t = -2.03$ and $P = 0.044$. Similar trends were observed for the left myocardial performance index by DTE with a mean of 0.79 ± 0.12 and 0.72 ± 0.12 for the case and control groups, respectively (t-3.32, $P = 0.001$). QT and heart rate by ECG and ET, IRT and MPI by DTE had significant differences in the case and control groups. LA in diastole and LVM and Peak A velocity had significant differences in both groups. ET, ICT, and IRT revealed significant differences in the case and control groups.
Conclusions: Consistent with many study's results, we reached the conclusion that Doppler Tissue Echocardiography and Conventional Echocardiography are good determination methods of systolic and diastolic myocardial functions in patients with celiac disease. Between these two methods, the present study confirmed the importance and strong power for Doppler Tissue Echocardiography.

1. 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 (1). It is a systemic immune-mediated disorder which is caused by a lasting intolerance of gluten, found in wheat, rye and barley. It is characterized by a wide range of clinical manifestations. Its prevalence ranged from 0.3% in Germany to 2.4% in Finland. It affects about 0.6 to 1.0%, of the world population. The prevalence of CD is 1.5 to 2 times higher in women than men and occurs in about 10 in1000 people in Europe and North America (2-4). 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. The incidence of CD increases in patients with primary and secondary

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cardiomyopathy (3, 4). 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 is able to be secondary to an immune response directed against an antigen present in both the myocardium and small intestine (2, 3, 5). 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. An immunologic associative mechanism and increased prevalence of CD in patients who have idiopathic dilated cardiomyopathy have been demonstrated (1, 6). Additionally, several reports have suggested that both CD and idiopathic dilated cardiomyopathy have an immune process with respect to the heart and intestine (3, 6, 7). It was found that there was an association between CHD and CD in two cases with coarctation of the aorta (8, 9). An increased risk of cardiovascular events and stroke in patients with CD has been confirmed by many studies. For instance, in two population-based studies, an increased risk of atrial fibrillation (AF) has been reported in patients with CD. It is also possible that cardiac rhythm disturbances such as AF may be associated with the observed increase in the risk of stroke (10, 11). The role of systemic inflammation in development of AF due to fibrotic changes in the atrium has been previously established (10). Doppler tissue echocardiography (DTE) assessment is a useful tool used for obtaining evidence of subclinical impairment of ventricular function during clinical stability in patients with CD (12). Akin performed a study on DTE and conventional echocardiography to evaluate the impairment of myocardial diastolic functions in patients with CD. They reached the conclusion that DTE was more accurate and reliable (12).

2. Objectives

The aim of the present study was to investigate cardiac functions in patients with celiac disease by using DTE and conventional echocardiography to identify myocardial dysfunctions in patients with celiac disease compared to healthy individuals using Doppler tissue echocardiography compared to conventional echocardiography.

3. Patients and Methods

3.1. Study Design and Samples

This case-control study was performed in a single-center with collaboration of gastroenterology and cardiology clinics from August 2015 to July 2016. The study was approved by the ethics committee of Zahedan University of Medical Sciences, Zahedan (ZaUMS), Iran. Consent form was obtained from the participants' guardians. Patients with celiac disease were aged 2 - 19 years old and diagnosed based on a combination of clinical findings and laboratory's tests (tTGIgA) with a cutoff point of 20 and confirmed by intestinal biopsy. After considering the exclusion criteria and confirmation by intestinal biopsy, 120 patients with celiac disease were enrolled in the study. The control group consisted of 60 healthy voluntary individuals with the same age and gender without any diseases. The following formula was applied to calculate the sample size.

$$n = \left(\frac{r+1}{r}\right)\frac{\sigma^2 (Z_\beta + Z_{\alpha 2})^2}{(d\text{ifference})^2}$$

n= Sample size in the case group, r = ratio of controls to cases = 0.5, σ = Standard deviation of the outcome variable = 1.58, Effect Size (the difference in means) = 0.7, Z_β , presents the power , typically 0.84for 80% power and $Z_{\alpha/2}$, presents the desired level of statistical significance , typically, 1.96 for 95% confidence interval.

3.2. Criteria

The exclusion criteria were patients with obvious valvular disease; rhythm abnormality;structural and congenital heart disease; active infection; malignancy; other systemic inflammatory diseases; diabetes mellitus; renal insufficiency; chronic obstructive pulmonary disease; and hypertension. The same exclusion criteria were applied for the control subjects.

3.3. Measures and Tools

The whole study population underwent ECG, conventional echocardiography and Doppler tissue echocardiography by one cardiologist using My Lab 60 instrument with 3-8-MHz transducers (made in Italy). ECG findings were as follows: 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). Rv5: (R wave in V5) the amplitude of R wave in the left Precordial lead.

Sv1: (S wave in V1) the amplitude of S wave in the right Precordial lead.

The means of all necessary echocardiographic parameters namely ejection fraction (EF), fractional shortening (FS), interventricular septal dimension in diastole (IVSDD), interventricular septal dimension in systole (IVSDS), left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD) posterior wall dimension in systole of the left ventricle (LVPWS), posterior wall dimension in diastole of the left ventricle (LVPWD), interventricular septal dimension in systole (IVSS), posterior wall dimension in systole (PWDS), and posterior wall dimension in diastole (PWDD) were measured via M-mode echocardiography of the left side estimated from three cardiac cycles.

The velocity of the blood flow through the heart valves, as well as the ejection time (ET), peak A velocity (A), peak E velocity (E), acceleration time (AT), deceleration time (DT), 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 (IRT), isovolumic contraction time (ICT) of both sides were measured with pulsed Doppler echocardiography (13).

The sample volume was positioned at the tip of the tricuspid and mitral valve leaflets in the apical four-chamber

view to enable the measurement of (a): which is the time interval between the end and start of trans-mitral and trans-tricuspid flow.

The sample volume was thereafter relocated in 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.

MPI or the Tie 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

All the parameters in the above formula were measured in the M-mode view and in diastole and utilized for the left ventricular mass evaluation (13, 14). Relative Wall Thickness (RWT) was calculated as 2 times PWd divided by the LVEDD (15). Doppler tissue echocardiography (DTE) was another method performed from the apical four-chamber view and a 3 mm pulsed Doppler sample volume was placed at the level of the lateral mitral annulus. 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) (Figure 1).

Our participants were weighted using RASA Mark made in Islamic Republic of Iran by error factor of 100 gr. In addition, their heights were measured in the standing position with a scale ruler.

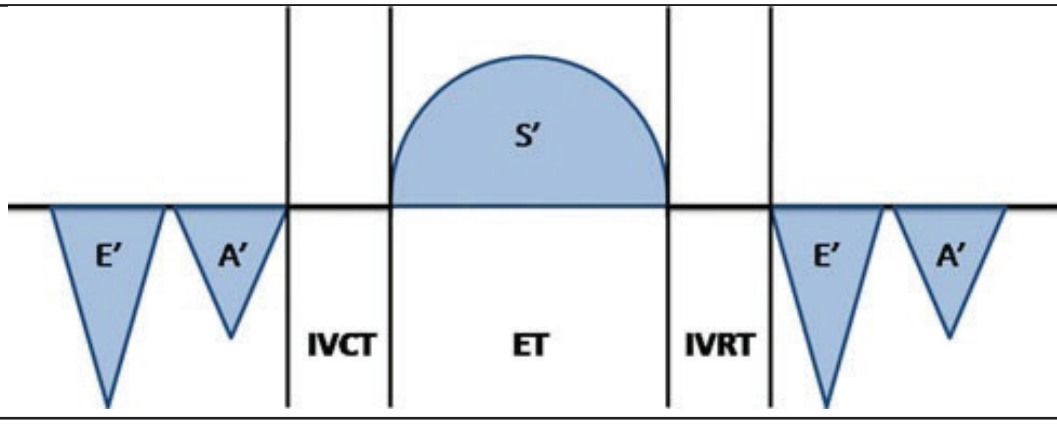
3.4. Statistical Analysis

Data were analyzed using SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc. The continuous variables were expressed as mean ± SD and nominal variables were expressed as number and percentages (%). The normal distribution of variables was verified through the Shapiro Wilk test. Student t-test was applied in the case of normality and the Mann-Whitney U test was applied in the case of non-normality distribution. The values were accepted as significant when $P < 0.05$.

4. Results

Normality distribution was examined by Shapiro-Wilk test, revealing that most of the variables had non-normal distribution. For this reason, non-parametric statistical test was used mostly. Sex distribution of the participants showed that from 120 patients, 67(55.83%) were females and for the controls it was 26(43.33%); this resulted in a sex matched trend in groups (P = 0.114). Table 1 illustrates that the participants were matched based on age (P = 0.319). Weight and height were significantly different between the two groups (P < 0.001) and (P = 0.003), respectively. It was found that 25 % of the participants were 14.78 kg and under 17.50 kg for the case and control groups, respectively. The median age for the case and control groups was 9 and 10 years, respectively. The

Figure 1. Diagram of Doppler Tissue Echocardiography Waves



S', systolic wave; E', early diastolic wave; A', late diastolic wave (16). Sv, Sm and St: Systolic myocardial velocity above the baseline in pulmonic vein, mitral and tricuspid. Ev, Em and Et: early diastolic myocardial relaxation velocity below the baseline in pulmonic vein, mitral and tricuspid. Av, Am and At: myocardial velocity associated with atrial contraction in pulmonic vein, mitral and tricuspid.

Table 1. Age, Weight and Height Case-Control Comparison

Variables	Groups	Mean	SD	First Quartile	Median	Third Quartile	P
Age	Case	8.90	3.80	6.00	9.00	12.00	0.320
	Control	9.43	3.82	6.00	10.00	12.00	
Weight	Case	22.29	8.50	14.78	20.75	28.88	< 0.001
	Control	28.82	11.29	17.50	30.00	34.38	
Height	Case	116.91	17.24	104.25	117.50	129.00	0.003
	Control	126.33	19.44	110.00	126.50	138.88	

first quartiles of height were lower in the case group (104.25) compared with the controls (110.00 cm).

Right ejection time (ET) had significant differences in the means (t = -2.03 and P = 0.044) of 245.30 ± 24.60 and 253 ± 22.66 for the case and control groups, respectively. Similar trends were observed for the left myocardial performance index by DTE with the means of 0.79 ± 0.12 and 0.72 ± 0.12 for the case and controls groups, respectively (t = -3.32, P = 0.001) (Table 2). ECG, conventional echocardiography and Doppler tissue echocardiography findings evaluation in the right heart showed that QT (P = 0.017) and heart rate (P = 0.030) by ECG, ET (P < 0.001), IRT (P = 0.012) and MPI (P < 0.001) by DTE had significant differences in the cases and controls (Table 3). LA in diastole (P = 0.041), LVM (P = 0.035) and Peak A velocity (P = 0.042) of the left heart had significant differences in the cases and controls due to conventional echocardiography (Table 4). Table 5 shows the results of the left heart findings by DTE in the case and control groups due to non-parametric test of Mann-Whitney U. The table revealed that ET (P < 0.001), ICT (P = 0.022), IRT (P = 0.015), Ev (P = 0.024), Av (P = 0.031) and Ev/Av (P < 0.001) had significant differences in case and controls.

Table 2. Conventional Echocardiography and Doppler Tissue Echocardiography Findings in Heart

Variables	Groups	N	Mean	SD	t value	P
A	Conventional Echocardiography				-0.36	0.719
	Case	120	413.03	43.80		
	Control	60	415.52	42.89		
Peak E velocity	Case	120	100.72	16.38	1.71	0.090
	Control	60	96.58	12.89		
AT	Case	120	423.70	51.29	-1.82	0.070
	Control	60	438.63	52.99		
ET	Case	120	240.73	21.89	-0.91	0.363
	Control	60	244.20	28.08		
FS	Case	120	0.43	0.06	-0.27	0.790
	Control	60	0.43	0.07		
Simpson EF	Case	120	45.12	8.51	-1.01	0.314
	Control	60	46.52	9.26		
MPI	Case	120	0.72	0.15	0.30	0.766
	Control	60	0.71	0.17		
Peak E/ peakE'	Case	120	6.81	1.57	0.42	0.674
	Control	60	6.70	1.64		
EF	Case	120	245.30	24.60	-2.03	0.044
	Control	60	253.00	22.66		
A	Doppler Tissue Echocardiography				-2.51	0.013
	Case	120	461.79	40.77		
	Control	60	477.48	36.92		
S'	Case	120	9.21	1.28	1.85	0.066
	Control	60	8.84	1.19		
A'(right)	Case	120	470.30	41.84	-1.16	0.249
	Control	60	477.67	37.05		
MPI	Case	120	0.79	0.12	3.32	< 0.001
	Control	60	0.72	0.12		

Abbreviations: a, is the time interval between the end and the start of trans-mitral and trans-tricuspid flow; peak E, early mitral valve flow velocity; At, Acceleration time; Et, ejection Time; FS, fractional shortening; Simpson EF, EF was calculated in the apical two and four chamber views with Simpson's apical biplane method; MPI, myocardial performance index; E / E', peak E velocity / Early diastolic myocardial relaxation velocity; S, Systolic myocardial velocity above the baseline in mitral and tricuspid.

Table 3. ECG, Conventional Echocardiography and Doppler Tissue Echocardiography Findings in the Right Heart

Variables	Groups	Mean	SD	First Quartile	Median	Third Quartile	P
ECG							
Rv_5	Case	8.27	2.31	7.00	8.00	9.00	0.735
	Control	8.50	2.20	7.00	8.00	10.00	
Sv_1	Case	4.21	2.00	3.00	4.00	5.00	0.969
	Control	4.47	2.56	2.00	3.50	7.00	
QT	Case	16.40	15.01	0.32	0.36	0.36	0.017
	Control	15.00	2.93	0.35	0.36	0.37	
Heart Rate	Case	97.00	18.82	80.00	99.50	109.50	0.030
	Control	91.00	18.58	76.25	91.00	100.75	
Conventional Echocardiography							
Peak E / peak A	Case	1.41	0.32	1.14	1.37	1.64	0.329
	Control	1.35	0.27	1.11	1.33	1.53	

MPI	Case	0.73	0.18	0.63	0.71	0.82	0.542
	Control	0.74	0.19	0.64	0.74	0.84	
AT	Case	64.33	11.12	56.00	61.00	72.00	0.172
	Control	62.00	10.94	56.00	61.00	70.75	
DT	Case	126.24	25.59	106.00	125.00	144.00	0.809
	Control	125.17	21.40	111.00	125.00	139.00	
Peak E velocity	Case	70.11	15.17	61.00	68.50	78.00	0.335
	Control	68.73	14.23	59.00	65.50	75.00	
Peak A velocity	Case	51.27	11.76	42.00	50.00	59.50	0.630
	Control	52.08	11.82	45.00	49.50	58.00	
Peak E/ Peak E'	Case	4.86	1.57	3.82	4.65	4.62	0.815
	Control	4.94	1.49	3.77	5.55	5.70	
Peak A/ Peak A'	Case	5.94	1.98	4.54	5.76	6.74	0.177
	Control	6.40	2.07	4.98	5.80	7.56	
Doppler Tissue Echocardiography							
ET	Case	111.78	21.69	228.00	244.00	256.00	0.001
	Control	103.10	17.84	268.25	284.00	311.50	
ICT	Case	11.70	2.25	72.00	78.00	89.00	0.179
	Control	11.65	1.84	62.50	78.00	82.25	
IRT	Case	9.14	2.28	94.00	111.00	128.00	0.012
	Control	8.53	1.87	90.00	106.00	117.00	
S'	Case	239.89	18.00	10.15	11.40	13.28	0.911
	Control	247.93	26.33	10.70	11.75	12.90	
A'	Case	10.90	2.42	7.50	9.20	10.48	0.06
	Control	10.70	1.94	7.30	8.60	9.90	
E'	Case	6.72	1.70	228.00	240.00	250.00	0.066
	Control	6.94	1.83	230.00	244.00	259.25	
E' / A'	Case	1.74	0.59	1.40	1.66	1.98	0.326
	Control	1.77	0.46	1.32	1.73	2.23	
MPI	Case	0.80	0.13	0.70	0.82	0.88	< 0.001
	Control	0.73	0.13	0.65	0.73	0.80	

Abbreviations: Rv5, (R wave in V5) the amplitude of R wave in left Precordial; Sv1, (S wave in V1) the amplitude of S wave in the right Precordial lead; 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, E/A; peak E velocity / Peak A velocity (ratio); MPI, myocardial performance index; At, Acceleration time; dt, deceleration time; E, early tricuspid valve flow velocity; A, late tricuspid valve flow velocity; E / E', peak E velocity / Early diastolic myocardial relaxation velocity; A / A', Peak A velocity / Myocardial velocity associated with atrial; Et, ejection Time; IRT, isovolumic relaxation time; ICT, isovolumic contraction time; St, Systolic myocardial velocity above the baseline in tricuspid; Et, early diastolic myocardial relaxation velocity below the baseline in tricuspid; At, Acceleration time

Table 4. Conventional Echocardiography Findings in Left Heart

Variables	Groups	Mean	SD	First Quartile	Median	Third Quartile	P
Aod	Case	1.97	1.51	1.65	1.82	2.00	0.650
	Control	1.87	0.31	1.61	1.85	2.10	
LAd	Case	2.24	0.40	1.96	2.18	2.45	0.041
	Control	2.34	0.38	2.09	2.40	2.61	
Aos	Case	1.73	0.73	1.50	1.68	1.82	0.646
	Control	1.72	0.33	1.46	1.69	1.90	
LAs	Case	1.67	1.26	1.36	1.50	1.75	0.198
	Control	1.62	0.32	1.40	1.57	1.84	
LVESD	Case	0.61	0.12	0.55	0.60	0.67	0.360
	Control	0.63	0.11	0.55	0.60	0.70	
LVEDD	Case	3.61	0.53	3.20	3.60	3.90	0.093
	Control	3.72	0.74	3.38	3.69	4.24	
PWDD	Case	0.34	0.06	0.30	0.35	0.38	0.086
	Control	0.36	0.06	0.32	0.36	0.40	
IVSSD	Case	0.83	0.14	0.72	0.81	0.91	0.023
	Control	0.88	0.16	0.77	0.85	0.94	
IVSDD	Case	2.07	0.43	1.75	2.08	2.30	0.569
	Control	2.25	1.10	1.73	2.10	2.48	
PWSD	Case	0.34	0.06	0.29	0.35	0.38	0.088
	Control	0.36	0.06	0.32	0.36	0.40	

EF	Case	0.74	0.07	0.71	0.74	0.79	0.967
	Control	0.74	0.08	0.69	0.75	0.80	
LVM	Case	37.38	17.95	24.25	35.00	47.75	0.035
	Control	44.38	21.61	26.50	44.00	55.00	
Simpson LVEDD	Case	45.64	18.41	32.00	41.50	56.50	0.248
	Control	49.91	21.52	35.38	44.50	63.00	
Simpson LVESD	Case	25.37	12.07	17.00	22.75	30.00	0.596
	Control	26.95	13.43	17.10	22.00	32.98	
LAd/Aod	Case	1.25	0.39	1.12	1.24	1.33	0.238
	Control	1.26	0.15	1.14	1.25	1.37	
LAs/Aos	Case	1.00	0.75	0.83	0.95	1.03	0.453
	Control	0.95	0.13	0.86	0.97	1.03	
Peak E /Peak A	Case	1.75	0.41	1.49	1.69	2.00	0.359
	Control	1.78	0.32	1.59	1.75	2.04	
LVMI	Case	24.70	8.65	18.01	23.75	30.04	0.086
	Control	27.17	12.01	19.51	27.27	33.31	
RWT	Case	0.19	0.04	0.17	0.19	0.21	0.745
	Control	0.22	0.16	0.17	0.19	0.21	
AT	Case	60.84	8.89	56.00	61.00	67.00	0.52 2
	Control	11.25	62.13	56.00	61.00	67.00	
DT	Case	131.38	27.46	111.00	133.00	150.00	0.464
	Control	135.35	30.58	117.00	128.00	158.25	
Peak A Velocity	Case	59.63	13.39	49.00	69.75	55.00	0.042
	Control	55.60	10.89	59.00	48.00	61.50	
Peak A/Peak A'	Case	8.33	2.14	6.84	8.12	9.81	0.915
	Control	8.39	2.06	6.79	8.12	9.91	
MPI	Case	0.71	0.15	0.60	0.72	0.81	0.851
	Control	0.71	0.17	0.58	0.71	0.82	

Abbreviations: Aod, Diameter of Aorta in Diastole; Lad, Diameter of LA in Diastole, Aos, Diameter of the Aorta in Systole; Las, Diameter of LA in Systole; IVSDD, interventricular septal dimension in diastole; LVDD, left ventricular end-diastolic dimension; PWDD, posterior wall dimension in diastole index; IVSDS, interventricular septal dimension in systole; LVSD, left ventricular end-systolic dimension; PWDS, posterior wall dimension in systole; EF, ejection fraction; LVM, Left ventricular mass; Simpson lvdd and Simpson lvsd; Lvdd and LVSD were calculated in the apical two and four chamber views with Simpson's apical biplane method; LAd/Aod, ratio of Diameter of LA in Diastole to Diameter of Aorta in Diastole; LAs/Aos, ratio of Diameter of LA in Systole to Diameter of the Aorta in Systole; LVMI, Left ventricular mass index; RWT, Relative Wall Thickness; AT, Acceleration time; DT, deceleration time; A; late mitral valve flow velocity; A / A', Peak A velocity / Myocardial velocity associated with atrial contraction; E/A, peak E velocity / Peak A velocity (ratio); MPI, myocardial performance index

Table 5. Doppler Tissue Echocardiography Findings in the Left Heart

Variables	Groups	Mean	SD	First Quartile	Median	Third Quartile	P
ET	Case	238.28	21.87	222.00	239.50	256.00	< 0.001
	Control	293.08	23.54	278.50	285.00	318.75	
ICT	Case	77.88	14.94	67.00	78.00	89.00	0.022
	Control	72.75	12.52	62.50	72.00	78.00	
IRT	Case	110.38	18.41	98.50	106.00	128.00	0.015
	Control	102.32	20.80	89.25	100.00	117.00	
Peak E velocity	Case	241.99	21.52	13.00	14.95	17.00	0.791
	Control	287.78	30.62	13.10	14.70	17.70	
Peak A velocity	Case	78.41	14.26	6.00	7.30	8.30	0.087
	Control	75.65	16.14	6.03	6.80	7.80	
MPI	Case	0.79	0.12	0.70	0.78	0.88	0.003
	Control	0.72	0.12	0.64	0.74	0.79	
Peak E / Peak A	Case	2.38	2.91	1.71	2.13	2.45	0.160
	Control	2.27	0.59	1.85	2.19	2.63	

Abbreviations: Et, ejection Time; IRT, isovolumic relaxation time; ICT, isovolumic contraction time; Em, early diastolic myocardial relaxation velocity below the baseline in the mitral valve; Am, myocardial velocity associated with atrial contraction in the mitral valve; Sv, Systolic myocardial velocity above the baseline in the pulmonic vein; Ev, early diastolic myocardial relaxation velocity below the baseline in the pulmonic vein; Av, myocardial velocity associated with atrial contraction in the pulmonic vein; Ev/Av, early diastolic myocardial relaxation velocity below the baseline in the pulmonary vein/early diastolic myocardial velocity associated with atrial contraction in the pulmonic vein; MPI, myocardial performance index

5. Discussion

Most of the patients with CD were female and the sex and age distributions were matched between the case and controls. Weight and height had lower values in patients. The results of the right heart findings showed lower trend of ET in patients. Left MPI by DTE was significantly higher in patients. In the right heart findings QT, the heart rate by ECG and ET, IRT and MPI by DTE were significantly different in the case and controls. The results of the left heartfindings by conventional echocardiography revealed that LA in diastole, LVM and Peak A velocity had significant differences, when in DTE, ejection time, ICT, IRT, Ev, Av and Ev/Av were different significantly. In a recent study, was found that CHD occurs more in inflammatory bowel disease (IBD) compared to general (17). Saylan et al. conducted a study on 75 children aged 5 months to 19 years to assess cardiac dysfunction in celiac disease compared with the controls. They reached the conclusion that the participants were in the same age and they had significant differences on weight and height that confirms our conditions. From the Saylan' et al.'s study also revealed that IVSD and LVEDD parameters were different between the patients and control group significantly (18). The present study concluded that only IVSS was different between the patients and controls when EF and FS were the same. These two parameters with MPI using conventional echocardiography had the same results in the present and Saylan et al.'s studies. Saylan et al. found a significant difference between the case and controls in Doppler tissue echocardiographic findings such as Em, Am, E (right), MPI (right), Sm, ICTm, A (right), and IRT (right) when the left IRT and left MPI were similar (18).

Results of the present study confirmed those of the left and right myocardial performance index (MPI) by Doppler tissue echocardiographic. It is noteworthy that Doppler tissue echocardiographic method was performed for pulmonary vein in which Peak E velocity and A velocity and their ratio (E/A) in the present study; the results were significant. Consistent with Saylan et al.'s study, the present research showed a powerful role of Doppler tissue echocardiographic method in this type of investigation. Akin et al. evaluated left ventricular functions using DTE and conventional echocardiography on patients with celiac disease. In this study, LVEDD, LVESD, PWd, IVSd, and EF parameters were not significant between patients and controls; this is similar to the present study findings. LA diameter in diastole had the same result in these two studies. Pulsed and continuous Doppler findings showed that mitral late diastolic flow (A) velocity and E/E' ratio were significantly higher in patients when the present study found that peak A velocity and E/E'(right) were similar and dissimilar, respectively. Moreover, E/A ratio was significantly lower in patients. In our study, when we used conventional echocardiography, the results were dissimilar, and IRT was significantly prolonged in the patients; this is inconsistent with our study. In their study, they also analyzed the left E'/A' ratio and IRT' by DTE, showing a low and high significant values in patients, respectively. In comparison with the present study, E'/A' was dissimilar and IRT' had the same trends. Myocardial performance index (MPI) is a parameter that displays both systolic and diastolic (global) performance of the ventricle. MPI had different trends in these two studies so that Akin et al. did not find any differences in the MPI ratio between the groups. In their study, DTE parameters such as left S', left E', and left E'/A' ratio were compared and the results revealed a lower level and for the left IRT' higher levels in the patients significantly, but the present study revealed a non-significant result for left S', left E', and left E'/A' ratio and a significant difference for the left IRT (12). Sari et al. applied conventional echocardiographic method to assess cardiac findings in the study population composed of patients with celiac diseases and controls. In their analysis, functions such as Ejection fraction, interventricular septum, posterior wall, left ventricular end diastolic diameter, left ventricular end systolic diameter, mitral E, mitral A and left atrium diameter were similar in the groups. They also applied strain–strain rate echocardiography methods for the left ventricular function in comparison to the two groups and found similar results between the groups. By using conventional echocardiography, the mentioned parameters showed the same results with our findings; instead of strain–strain rate echocardiography methods, we applied DTE (5). Cow's milk allergy (CMA) is an immunological reaction to one or more milk proteins and this occurs due to reactions mediated by Th1 cells, interactions between T lymphocytes, and mast cells and neurons that alter the function of the smooth muscle and intestinal motility (19). Lee et al. (20) conducted a study to compare the heart function in children with cow's milk allergy and controls. They compared the left and right ventricle echocardiographic findings in the groups. Using the basic method, we considered the functions of interventricular septum thickness in the diastole, left ventricular end-diastolic diameter and posterior wall thickness in diastole for the analysis and it was found that all were similar in the groups; likewise, they were similar in the present study related findings. Ece et al.'s study also concluded that the left ventricle echocardiographic findings by DTE, i.e. peak E' velocity, E'/A', E/E', IRT, DT and MPI, had non-significant differences between the groups and in the case of right ventricle echocardiographic findings, E' velocity, A', E'/A', IRTs and MPI were significantly different between the two groups. In the present study, it was revealed that IRT, ICT and MPI were significantly higher in patients compared with the controls in the left and right heart. Other functions had different results from those of Ece et al.'s study. In infants with cow's milk allergy, the fact that the impairments of diastolic function are unknown can be explained by the hypothesis that abnormal intestinal permeability in patients with cow's milk allergy is due to increased systemic absorption of various luminal antigens or infectious antigen that may cause myocardial damage through immune-mediated mechanisms (21). Therefore, in the patients with cow milk allergy, permeability of intestinal abnormality occurs related to systemic absorption of various luminal antigens or infectious agents that all might cause an impairment in the myocardial function among immune-mediated mechanisms. These theories can be those mechanisms for celiac disease. Bayar et al. performed a study on patients

with CD and controls to assess the left atrial function. The results of the study showed that the means of left ventricular EF, IVS thickness, posterior wall thickness, LA diameter, LVEDD, LVESD, and systolic pulmonary artery pressure values were within the normal ranges in both patients and control (10). All the parameters assessed by Bayar had similar trends with our findings except for LA diameter in diastole. Karadas et al. (22) performed a study on children with CD to evaluate cardiac involvements using conventional and DTE and showed that from all the heart functions used in the study only left E/E' was significant in both methods. In contrast, in the present study left E/E' showed different result. In the present study, functions such as LA dimeter in diastole, I VSS diameter in systole, LVM, peak A velocity by conventional echocardiography and ET, ICT, IRT by DTE methods revealed significant differences between the CD children and control when these functions in the mentioned study had similar values between the groups. In addition, in Karadas et al.;s study, MPI had a similar trend in the case and control groups due to both DTE and conventional cardiography. This result was similar to ours using conventional echocardiography, but the values of MPI in the present study were different significantly in both left and right heart through application of DTE. Moreover, Polat et al. (23) conducted a study on celiac children to compare their heart functions with the controls; based on categorization of patients in their study, many of the functions had different values compared with the controls in the case of positive serologic test. The significant functions were LVDD, LVSD, LA diameter in diastole, EF, peak S', peak E', peak A' velocity and E'/A'. The majority of the heart functions in the Ploat's study were similar to those of the present study, especially the results using DTE method. Dissimilarity with our study was related to MPI. Despite all the points discussed above, the present study contributed to literature by proving that diastolic dysfunctions is dominant and is an important early finding in celiac patients. In this regard, the present study demonstrated more efficacy of DTE in determination of the cardiac involvements in celiac disease compared to other methods.

5.1. Conclusions

Our study showed that Doppler Tissue Echocardiography had more accurate results compared with the other two methods in comparison with various studies. Despite many reports, Doppler Tissue Echocardiography and Conventional Echocardiography are valuable methods to assess systolic and diastolic myocardial functions in patients with celiac disease, but the present study confirmed that Doppler Tissue Echocardiography is better. Furthermore, the study also found that an increase in the myocardial performance index could be measured by DTE better than Conventional Echocardiography. The present study suggests that DTE has better status in comparison with conventional echocardiography to identify asymptomatic patients in early stages of cardiac involvements.

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Authors' Contribution

Noormohammad Noori supervised the study and controlling writing, Turan Shahraki prepared the data, Alireza Teimouri performed the data analysis and writing the parimary version of the manuscript and Iraj Shahramian contribute in data collection.

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