The subclinical effect of celiac disease on the heart and the effect of gluten-free diet on cardiac functions

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SUMMARY: Karadaş U, Eliaçık K, Baran M, Kanık A, Özdemir N, İnce OT, Bakiler AR. The subclinical effect of celiac disease on the heart and the effect of gluten-free diet on cardiac functions. Turk J Pediatr 2016; 58: 241-245.

This study aimed to investigate the effects of celiac disease (CD) on cardiac function in children by using conventional transthoracic echocardiography (TTE) and tissue Doppler echocardiography (TDE). Forty-nine patients diagnosed with CD were enrolled into the study. Group 1 consisted of 26 (53%) patients who had recently been diagnosed and had not been on gluten-free diet whereas Group 2 consisted of 23 (47%) patients who had been on regular gluten-free diet for at least 10 months. 20 healthy children were enrolled into the study as the control group. The deceleration time (DT) and the left ventricle (LV) isovolumetric relaxation time (IVRT) were significantly shorter in Group 1 compared to Group 2 and the control group (p=0.002, p=0.015). Mitral valve E/E' ratio was significantly lower in Group 1 and 2 when compared to the control group (p<0.001). The study demonstrated that evaluation of these parameters by using TDE could be beneficial in the early diagnosis of cardiac involvement in children with CD.

Key words: celiac disease, tissue Doppler echocardiography, gluten free diet.

Celiac disease (CD) is a chronic inflammatory condition caused by immune pathology in small intestines in genetically susceptible individuals[1]. Gastrointestinal system problems such as malabsorption, chronic diarrhea, and abdominal pain are common in CD. Besides, cardiovascular system pathologies such as myocarditis and idiopathic dilated cardiomyopathy (IDCM) have also been found to be associated with CD[2]. These studies about CD suggest that subclinical involvement of cardiovascular system **is** much more frequent than IDCM and myocarditis[3,4].

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[5-8]. However, the number of studies on TDE's role in analyzing cardiac functions, and the spectrum and frequency of cardiac involvement in children with CD is limited[9,10].

In this study, 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.

Materials and Methods

This study was conducted between July 2012 and January 2015 at Izmir Tepecik Research and Training Hospital as a cross-sectional cohort study. The research procedure was approved by the local ethical committee. Parents were informed about the study and each parent provided a written consent to allow their child to participate in the study.

Forty-nine patients with CD who had been diagnosed according to the diagnostic criteria of the 2012 European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [11] were enrolled in the study. Group 1 consisted of 26 (%53) patients who had recently been diagnosed and had not been

on gluten-free diet, whereas Group 2 consisted of 23 (47%) patients who had been on regular gluten-free diet for at least 10 months, and the control group 20 had healthy children. The data obtained from conventional echocardiography and TDE performed in all three groups were compared with each other.

The same pediatric cardiology specialist performed the echocardiographic examination by using Philips Ultrasound System and an S 3-1 probe. Patients with congenital and/or acquired heart diseases were excluded from the study. Conventional echocardiographic measurements were made according to the American Echocardiography Society[12] standards. The dimensions of the left ventricle in the parasternal long axis on M mode tracing, and ejection fraction (EF) and fractional shortening (FS) were analyzed by using the Teicholz formula[13]. Peak early filling velocity (E wave), peak atrial systolic velocity (A wave), early-to-late diastolic flow ratio (E/A) and deceleration time (DT) measurements were made. Isovolumetric relaxation time (IVRT) was measured through the mitral valve (MV) which was placed on the myocardial segment on the left ventricle septal and posterior wall and at the edge of the cursor valve on the apical four chamber view by using TDE.

This method helped in obtaining the E' (early diastolic mitral annular velocity which was measured separately on the left ventricular septum and its posterior wall, and the average of which was taken into consideration), A' (late diastolic mitral annular velocity which was measured separately on the left ventricular septum and its posterior wall, and the average of which was taken into consideration), E'/A' and E/E' ratios. The left ventricle's myocardial performance index (a' time: time between late diastolic myocardial velocity (A') and early diastolic myocardial velocity (E'), b' time: peak myocardial velocity during systole, and the myocardial performance index: (a'-b')/b') were calculated.

The data were analyzed using the SPSS (Statistical Package for Social Sciences) program (version 17.0). The average values and the standard deviation were calculated. The categorical data were compared with one another using the chi-square test for the statistical analysis. Because neither group was normally distributed, comparison between the groups was made by using Mann-Whitney U-test. The differences between the three groups were evaluated by using the Kruskal-Wallis variance analysis and the findings were considered significant if a *p* value <0.05.

Results

The celiac groups (Groups 1 and 2) consisted of 49 patients, 26 (52%) of which were girls with an age average of 9.5±4 years whereas the control group consisted of 20 patients, 11 (55%) of which were girls with an age average of 9.1±3.4 years. There was no difference between the patient and the control groups regarding their gender and age (*p*=0.789, *p*=0.588).

The average follow-up period for the patients in Group 2 was 36.3±25.2 months (range: 10-126). The mean hemoglobin level in Group 2 was significantly higher compared to Group 1 (*p*=0.014) (Table I).

Regarding the echocardiographic findings of the Group 1 and Group 2 compared with the control group, MV E/E' ratio was significantly lower in

Table I. The Comparison of Clinical and Laboratory Features of Group 1 and Group 2.

	Group 1 (n=26)	Group 2 (n=23)	*P*
Age (years)	7.9±3.5	11.8±4.1	<0.001
Sex (F/M)	13/13	13/10	0.509
Heart rate (/min)	101±10	94±12	0.274
Height (cm)	120.3±19.1	134.5±21	-
Weight (kg)	23.5±9.8	33.4±13.3	-
Hemoglobin (g/dl)	10.9±1.6	12±1.4	0.014
Albumin (g/dl)	4.09±0.4	4.28±0.6	0.202

Table II. The Comparison of Conventional and Tissue Doppler Echocardiography Results of the Celiac and Control Groups

	Celiac group (n=49)	Control group (n=20)	*P*
EF	69.3±4.8	69.4±3.8	0.877
FS	38.3±3.9	38.5±3.2	0.792
MV E	1.1±0.16	1.03±0.17	0.126
MV A	0.65±0.15	0.58±0.19	0.387
MV E/A	1.73±0.40	1.77±0.55	0.994
MV E′	0.16±0.03	0.16±0.03	0.991
MV A′	0.082±0.02	0.076±0.01	0.353
MV E′/ A′	2.13±0.6	2.23±0.54	0.548
MV E/ E′	6.84±1.25	10.4±2.8	<0.001
DT	0.132±0.03	0.143±0.12	0.574
LV MPI	0.185±0.13	0,196±0.20	0.222
MV IVRT	0.068±0.07	0.070±0.011	0.846

DT: deceleration time, EF: ejection fraction, FS: fractional shortening, LV MPI: left ventricle myocardial performance index, MV E: peak early filling velocity, MV A: peak atrial systolic velocity, MV E′: mitral valve early diastolic velocity, MV A′: mitral valve late diastolic velocity, MV IVRT: Isovolumic relaxation time.

Table III. The Comparison of Conventional and Tissue Doppler Echocardiography Results of Group 1, Group 2 and the Control Group

	Group 1 (n=26)	Group 2 (n=23)	Control group (n=20)	P
EF	69.3±4.5	68.9±4.5	69.4±3.8	0.989
FS	38.2±3.6	37.8±3.4	38.5±3.2	0.876
MV E	1.1±0.15	1.07±0.16	1.03±0.17	0.185
MV A	0.68±0.1[a]	0.60±0.11 [a]	0.58±0.19	0.157
MV E/A	1.67±0.38	1.80±0.34	1.77±0.55	0.415
MV E′	0.163±0.03	0.146±0.031	0.16±0.03	0.069
MV A′	0.080±0.02	0.075±0.2	0.076±0,01	0.378
MV E′/ A′	2.12±0.6	1.94±0.51	2.23±0.54	0.109
MV E/ E′	7±1.25[b]	7.8±3.14[c]	10.4±2.8	<0.001
DT	0.117±0.03[d,e]	0.148±0.03 [d]	0.143±0.12	0.002
LV MPI	0.209±0.12	0.194±0.12	0.196±0.20	0.743
MV IVRT	0.054±0.14[f,g]	0.065±0.15 [g]	0.070±0.011	0.015

DT: deceleration time, EF: ejection fraction, FS: fractional shortening, LV MPI: left ventricle myocardial performance index, MV E: peak early filling velocity, MV A: peak atrial systolic velocity, MV E′: mitral valve early diastolic velocity, MV A′: mitral valve late diastolic velocity, MV IVRT: Isovolumic relaxation time.
a: Group 1 and Group 2 statistically significant (p=0.045), b: Group 1 and control group statistically significant (P<0.001)
c: Group 2 and control group statistically significant (P<0.001), d: Group 1 and Group 2 statistically significant (p=0.002)
e: Group 1 and control statistically significant (p=0.002), f: Group 1 and control statistically significant (p=0.015),
g: Group 1 and Group 2 statistically significant (p=0.015)

CD patients (*p*<0.001). Other conventional and tissue Doppler echocardiographic measurements were all normal without any significant difference between the groups (Table II).

When we compare the echocardiographic findings of Group 1 and Group 2, the DT and IVRT were significantly shorter in Group 1 compared to Group 2 and the control group (*p*=0.002, *p*=0.015). Mitral valve E/E′ ratio was significantly lower in Group 1 and 2 compared to control group (*p*<0.001). No systolic dysfunction or cardiomyopathy was encountered among the children in our study group (Table III).

Discussion

This study investigates the early pathological findings of cardiac involvement in children with CD by using TDE and compares these cases with healthy subjects. The TDE findings revealed that diastolic dysfunction is the earliest cardiac complication of pediatric CD. Different theories have been put forward to explain the reasons of cardiac involvement in Celiac disease[14,15]. One theory explains it with nutritional deficiency triggered by intestinal malabsorption, whereas another points to inflammatory response in myocardial tissue caused by activation of the immune system by increased absorption of numerous antigens following increased intestinal permeability[14,16,17].Tissue Doppler echocardiography can be used to evaluate the subclinical involvement of ventricular functions secondary to increased myocardial inflammation in CD, as well as to detect the cardiac functions in the early phase of CD[3]. However, the number of studies that demonstrate the role of TDE in subclinical cardiac involvement of pediatric CD[10,18] is limited.

The normal diastolic function can be identified as the effective and full filling of the left ventricle under physiological pressure regardless of age. The left ventricle diastole starts with the closing of the aortic valves and the period between the closing of aortic valves and the opening of mitral valves is termed as isovolumetric relaxation. After the isovolumetric relaxation, mitral valves open and the most of the filling occurs in the first 1/3 of diastole (early rapid ventricular filling). This stage is termed as E wave. The mitral annulus movement accompanies to this early filling. This interval is measured in Doppler echocardiography (E'). A small filling may be seen in the middle of the diastole. This period is termed as diastasis. This is followed by atrial systole (A wave) which causes a small amount of additional filling. The diastolic function is evaluated by IVRT, DT, E/A, and E/E'[19].

TDE parameters; DT and IVRT were significantly shorter in Group 1 compared to Group 2 and the control group ($p=0.002$, $p=0.015$) which indicates diastolic cardiac dysfunction. The first indicator of diastolic dysfunction is impaired relaxation[19]. Secondary to impaired relaxation is IVRT and DT shortening triggered by the decrease in the left ventricular compliance. This tells us that that, IVRT and DT are the early

predictors to show diastolic dysfunction and early cardiac involvement. The level of IVRT (70-90) <70 millisecond (ms), the level of DT (N: 140-240) <140 ms means restrictive pattern (impaired relaxation) and helps to show diastolic dysfunction[19].

As to the TDE findings, MV E/E' ratio was significantly lower in Groups 1 and 2 compared to the control group (p<0.001). None of the patients had a MV E/E' ratio over 15. However, the average of this ratio was below 8 in the patients with CD (Group 1 and 2), and it was significantly different than that of the control group (p<0.001). The proportion of the peak early filling velocity (E) to the early diastolic mitral annular velocity (E') is measured by Doppler (E/E', N: 5-10). Accordingly, <8 is deemed to show early diastolic dysfunction, whereas>15 is considered to show impaired diastolic function[19]. Therefore, MV E/E' ratioas well as the measurement of DT and IVRT may help to show the diastolic cardiac involvement in the children with CD.

Consistent with our findings, in a study conducted on 45 patients with CD, Polat et al.[10] reported that subclinical deterioration was observed in systolic functions (reduction in myocardial systolic valve velocity of the mitral annulus and gradual increase in contraction time and myocardial pre-contraction of the left ventricle). Cevik et al.[3] reported that, the TDE parameters of LV myocardial performance index (MPI) and LV IVRT were effective in patients with CD.

Lionetti et al.[4] reported moderate cardiac involvement in 13 patients (mitral, aortic, pulmonary and tricuspid valve deficiency or decreased ejection fraction) in a study with 60 celiac patients. They reported an improvement in echocardiographic findings in patients who were on a gluten-free diet. Curione et al.[16] reported IDCM in 3 patients with CD, and in 2 of the patients, the echocardiographic findings improved after 28 months of gluten-free diet. Chiccoet al.[20] diagnosed 3 CD (%2.9) among a series of 104 IDCM patients and they have found a recovery in the left ventricular ejection fractions with the gluten-free diet. Unlike the findings in the present literature, no systolic dysfunction or valve deficiency were found in our study group with conventional echocardiography. In the newly diagnosed (Group 1) celiac patients, DT and IVRT were

significantly shorter when compared to the patients on a gluten-free diet (Group 2) ($p=0.002$, $p=0.015$, respectively) and the diastolic cardiac function parameters were much more affected in the newly diagnosed Celiac patients.

The limitations of our study are the sample size and the cross-sectional design of the study. 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. Future studies could examine the effect of gluten-free diet with a larger sample. Despite these shortcomings, the study contributed to the literature by demonstrating that diastolic dysfunction is an important early finding in the children with CD. Furthermore, we showed the efficacy of TDE for the determination of the subclinical early stage of cardiac involvement in pediatric CD.

Conclusion

The results suggested that measuring the MV E/E′ ratio, DT and LV IVRT parameters by TDE could be beneficial in the early determination of the cardiac involvement. Therefore, monitoring these parameters during the follow up may help to show the effectiveness of treatment in children with CD.

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