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ARAŞTIRMA / RESEARCH

Determination of early atherosclerosis risk with aortic elasticity parameters in children with subclinical Celiac disease

Subklinik Çölyak hastalığı olan çocuklarda erken ateroskleroz riskinin aortik elasitisite parametreleri ile belirlenmesi

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Abstract

Purpose: The aim of this study was to evaluate increased aortic elasticity parameters and myocardial function in children with celiac disease (CD) and the effect of the subclinical myocardial damage on the elasticity parameters.

Materials and Methods: Fiftytwo children with CD and 60 healthy subjects were included in the study. Patients were divided into two groups according to IgA-tissue transglutaminase (IgA-tTG) antibody results. All children's cardiac functions were assessed by conventional echocardiography and tissue Doppler (TDI) imaging. Aortic strain, distensibilty and stiffness index (SI) were calculated by M-mode echocardiography.

Results: Isovolumetric contraction time and isovolumetric relaxation time values and myocardial performance index (Tei) evaluated for both ventricles by TDI were significantly higher in patients. Right ventricle Tei index value was the highest in the group of serum IgA-tTG antibody positive. Patient group exhibited significantly lower strain values and higher SI than the controls.

Conclusion: Our study showed that aortic elasticity parameters in children with subclinical CD are related to arterial pressure and may be used to determine increased prematurity atherosclerosis risk. These results suggest that serious cardiovascular complications can be predicted with echocardiographic follow-up especially in children with antibody-positive CD.

Key words: Celiac disease, tissue Doppler echocardiography, IgA-tissue transglutaminase.

Öz

Amaç: Bu çalışma çölyak hatsalığı (ÇH) olan çocuklarda artmış aortik elastisite parametrelerinin ve miyokard fonksiyonlarının birlikte değerlendirildiği ve subklinik myokard hasarının esneklik parametreleri üzerine etkisinin incelenmeyi amaçlamıştır..

Gereç ve Yöntem: Çalışmaya 52 CH ve yaş ve cinsiyet yönünden benzer 60 sağlıklı çocuk alındı. Hastalar antitissue transglutaminase (anti-tTG) antibody sonuçlarına göre iki gruba ayrıldı. Tüm çocukların kardiyak fonksiyonları konvensiyonel ekokardiyografi ve doku Doppler (TDI) görüntüleme yöntemiyle değerlendirildi. M-mode ekokardiyografi ile aortik strain, distensibilite ve stiffness index (SI) hesaplandı.

Bulgular: Hastaların demografik verileri ve laboratory characteristics kontrolere benzerdi. Her iki ventrikül için TDI ile değerlendirilen ICT and IRT values ve Tei index anlamlı yüksekti. RV Tei index value was the highest in the group of serum anti-tTG antibody pozitive. Patient group exihibited significantly lower strain values and higher SI than the controls.

Sonuç: Bu çalışma subklinik CD'li çocuklarda aortik elastisite parametreleri ile prematür ateroskleroz riskinin arttığı ve bunun arteriyel basınç ile ilişkili olduğunu gösterdi. Bu sonuçlar özellikle antikor pozitif CD'li çocuklarda ekokardiyografik izlem ile oluşabilecek ciddi kardiyovasküler komplikasyonların öngörülebileceğini düşündürmektedir.

Anahtar kelimeler: Çölyak hastalığı, doku Doppler echocardiography, doku transglutaminaz-IgA.

INTRODUCTION

Celiac disease (CD) is a chronic immune-mediated inflammatory disease of the small intestine that develops susceptibility to the gliadin and related proteins in the diet in genetically predisposed

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individuals[1]. It is estimated that CD affects at least 1 out of every 133 people in the population[2]. The resulting immunological response is not limited to the intestine and can affect different organs including the heart although the exact mechanisms are unknown[3]. There is an increased frequency of autoimmune myocarditis and idiopathic dilated cardiomyopathy in patients with CD because of the impaired immunological response[4,5]. Two epidemiological studies conducted in Scandinavian countries showed that the risk of death due to the cardiovascular disease in patients with CD is higher than those in the general population[6,7]. However, there is a limited number of studies related to other cardiac disorders in CD such as atrial fibrillation, myocarditis, atherosclerosis and ischemic heart disease[8,9]. There is very little data showing that children with CD have increased risk of vascular deterioration and atherosclerosis[10,11].

In the early diagnosis of atheroma, the aortic elasticity parameters in which the mechanical properties of the aorta are assessed by noninvasive methods are of great benefit[12]. Increased aortic stiffness or decreased distensibility can be used as a marker of widespread atherosclerotic involvement of the vascular system[12]. Tissue Doppler imaging (TDI) is a new, noninvasive and simple method of echocardiography that can assess global ventricular systolic and diastolic functions with a higher sensitivity than the conventional echocardiography in detecting subclinical myocardial injury[8,9]. In children with CD, there are few studies showing subclinical cardiac dysfunction with TDI. To the best of our knowledge, the risk of early atherosclerosis in children with CD was not previously examined using aortic elasticity parameters. The aim of this study is to evaluate the increased aortic elasticity parameters and myocardial function in children with CD and determine the effect of the subclinical myocardial injury on the elasticity parameters.

MATERIALS AND METHODS

Fifty-two children (under 18 years old), who are being followed by our pediatric gastroenterology department with a diagnosis of CD, were selected as the patient group. The diagnosis of CD in all patients was made based on the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) criteria[13]. All patients were diagnosed as CD based on the small intestinal biopsy specimens obtained by upper gastrointestinal endoscopy. Histopathological examination of the duodenal biopsies from all patients showed shortening of the villi, crypt hyperplasia, and an increased number of intra-epithelial lymphocytes according to the modified Marsh classification[14]. The control group included age, gender, and body surface area matched 60 healthy children who were evaluated to investigate the etiology of cardiac murmur and determined to have normal cardiac findings.

Children with CD (patient group) were divided into two different groups at the time of echocardiographic evaluation: Group 1 was positive for serum IgA-tissue transglutaminase (IgA-tTG) antibody (n=31), and group 2 was negative for serum IgA-tTG antibody (n=21). The cardiac functions of all children in this study were evaluated using conventional echocardiography, and TDI methods. The study protocol was approved by the local Ethics Committee (2017/300).

Echocardiographic study

Transthoracic echocardiography, performed via Vivid E9 Pro Ultrasound System (GE Medical Systems, Canada) by using 3 and 6 MHz transducers as 2D, M-mode and colored Doppler, conventional continuous-wave (CW) and pulse wave (PW) Doppler visualizing methods. Each study was performed at rest and in supine position without sedation to confirm normal anatomy and function. Echocardiographic measurements were obtained, and left ventricular structure, and systolic and diastolic function have been determined according to the pediatric guidelines of the American Society of Echocardiography[15].

Aortic annulus (AAn), aortic root (AR), and sinotubular junction (STJ), were measured at mid-systole and end-diastole using the inner-to inner edge method in a 2D parasternal long-axis view (16). The diameter of the proximal ascending aorta (AAO) was measured at 2–3 cm from the valve at end systole and end-diastole using the leading edge to leading edge principle in M-mode. Z-scores were used for data analysis as appropriate. A z-score >2 was considered dilatation. All echocardiographic measurements were averaged from 3 consecutive heartbeats. Systolic and diastolic blood pressures were measured in the right arm by

sphygomanometer with the patient in a supine position. Aortic strain (AS), aortic distensibility (DIS), and aortic stiffness index (SI) were derived from previously described formulas[16].

Aortic distensibility=2×(AOs–AOd)/(AOd)×(SBP–DBP)
Aortic strain (%)=100×(AOs–AOd)/AOd
Aortic stiffness index (β)=ln(SBP/DBP)/([AOs–AOd]/AOd)
(Where AOs and AOd are the systolic and diastolic aortic dimensions, respectively, and ln is the natural logarithm)

In the apical four-chamber view, the pulsed Doppler sample volume located between the tips of the mitral and tricuspid valve leaflets during diastole. The early diastolic flow (E-wave) and late diastolic flow (A-wave) velocities, and the E/A ratio were calculated from recordings, and the deceleration time of the E-wave was measured. The early diastolic (E′-wave), late diastolic (A′-wave), and systolic (S′-wave) velocities were measured throughout a cardiac cycle at mitral and tricuspid lateral annulus and at basal septal wall at apical 4-chamber views by pulsed-wave TDI. Then, the left ventricular (LV) Tei and right ventricular (RV) myocardial performance index (Tei indexes) were calculated.

Statistical analysis

The data were processed and analyzed using the STATA MP/11 (Stata Corp LP 4905 Lakeway Drive College Station TEXAS 77845) statistical package. These variables were summarized as mean and standard deviation and the comparisons between patient and control groups were performed using independent t-test or Mann-Whitney U test. The groups were also checked by Levene test for variance homogeneity. Statistically significance level was assessed as less than 0,05. The comparisons for categorical variables were done using chi-square test. When this data type was summarized, numbers and percentage values were used. Pearson correlation coefficient was used to evaluate the relationship between continuous parameters. Regression analysis was performed for the variables with statistically significant linear correlation and the regression equation was established.

RESULTS

In this study, 52 patients (38 female/ 14 male) with a diagnosis of CD and age, sex, and body surface area matched 60 healthy children (39 female/21 male) were included. The mean age of the patients was 12.1 ± 3.8 years. The patients with CD were divided into two groups based on their serum IgA-tTG titer (31 were positive for IgA-tTG and 21 were negative of anti-tTG).

The mean follow-up time was 4.20±2.12 years. Clinicoepidemiologic data, systolic and diastolic blood pressure and laboratory characteristics of the patient and control groups were shown in Table 1. Conventional M-Mode echocardiography results of the patient and control groups are shown in Table 2. Conventional echocardiography measurements did not differ between the groups. The LV systolic and diastolic diameters were similar in the groups (Table 2). Besides, we found that the LV ejection fraction was similar and in the normal range in the groups.

In the patient group, we found significantly lower mitral systolic (Sm) wave velocity, mitral annular Em wave velocity, mitral annular Am wave velocity values ($P < 0.05$), and higher mean E/Em ratio ($P=0.001$) than those in the control group. In addition, patients with CD had significantly prolonged Isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) values, and consequently higher LV Tei index values ($P <0.05$). Tricuspid annular Sm wave velocity ($P=0.003$), Em wave velocity ($P=0.015$) were lower and mean E/Em ratio ($P=0.001$) were higher in both (IgA-tTG antibody negative group and IgA-tTG antibody positive group) patient groups separately with CD when compared to controls. In addition, both patient groups had prolonged ICT and IRT, and higher RV Tei index value ($P < 0.001$).

In addition, RV Tei index was significantly higher in the IgA-tTG antibody positive group than the IgA-tTG antibody negative group. Tricuspid annular Am wave velocity showed no significant difference in patients with CD compared to control group. TDI measurements and LV and RV Tei indexes of the groups were shown in Table 3.Aortic strain values were significantly lower in the patient group than in the control group ($P =0.033$). The mean SI was significantly higher in the patient group than in the controls ($P =0.048$). There was no significant difference in aortic distensibility index (Table 2). In patient group, there was a negative correlation between strain values and systolic and diastolic blood pressure, while there was a positive correlation for SI. However, no correlation was

established between parameters of TDI, blood lipid levels and ascending aortic elasticity. The correlation between elasticity parameters and systolic and diastolic blood pressure in pateint group were shown Table 4. The aortic elasticity indexes were similar in both patient groups, but strain values were significantly lower in the group of serum IgA-tTG antibody positive than in the control group (P =0.038). The mean SI was significantly higher in the group of serum IgA-tTG antibody positive than in the controls (P =0.018). However, we found no statistical significance between serum IgA-tTG antibody negative group and control group. The mean follow-up time was similar in both (IgA-tTG antibody negative and IgA-tTG antibody positive) groups and no significant correlation was found between the follow-up period and the echocardiographic parameters.

Table 1: Clincoepidemiologic data and laboratory characteristics of the patients and control groups

	Patients (n=52)	**Controls (n=60)**	**P value**
Age (years)	12.10±3.85	11.05±3.48	0.133
Sex (female/male)	38/14	39/21	0.474
Weight (kg)	37.31±14.87	40.65±14.95	0.239
Height (cm)	140.98±20.51	146.37±18.99	0.152
Body surface area (kg/m²)	17.84±3.67	18.24±3.25	0.540
Blood Pressures			
Systolic	101.83±10.29	102.92±10.66	0.585
Diastolic	63.56±10.25	65.42±10.10	0.337
Heart Rate (beat/mean)	78.83±14.09	81.43±16.19	0.369
Laboratory characteristics			
Hgb (gm/dL)	12.76±1.27	12.88±1.22	0.608
ESR	5.63±3.44	5.59±4.84	0.949
CRP	1.69±1.66	2.27±3.10	0,051
AST (IU/L)	24.58±20.43	25.29±8.03	0.816
ALT in (IU/L)	13.53±6.65	14.25±4.23	0.492
T.Col (mg/dl)	148.10±22.49	145.71±30.32	0.634
LDL Col (mg/dl)	73.11±26.77	72.58±20.78	0.907
HDL Col (mg/dl)	50.10±12.43	53.78±12.05	0.115
Triglyceride (mg/dl)	98.11±43.84	88.30±48.28	0.262

(AST: aspartate aminotransferase; ALT; Alanine aminotransferase; ESR: Erythrocyte sedimentation rate; CRP: C reactive protein; Hgb: Hemoglobin; HDL:high density lipoprotein; LDL: Low density lipoprotein; T Col: total cholesterol)

Table 2. Conventional echocardiographic measurements and aortic elasticity indexes of study groups.

	Patients (n=52)	**Controls (n=60)**	**P value**
LVEDD	37.46±5.07	37.05±4.80	0.661
LVESD	23.78±3.50	23.51±3.86	0.700
EF	67.19±5.53	67.31±6.38	0.913
LV FS %	36.60±4.39	37.03±5.55	0.722
Mitral inflow			
E wave (cm/s)	9.90±1.21	9.32±1.42	0.051
A wave (cm/s)	6.17±1.04	6.17±1.04	0.058
E/A ratio	1.47±2.29	1.37±2.04	0.358
Tricuspid inflow			
E wave (cm/s)	8.17±1.34	7.97±1.07	0.367
A wave (cm/s)	6.12±1.36	6.25±1.38	0.614
E/A ratio	1.37±2.45	1.32±2.37	0.218
Distensibility (x10-3mmHg-1)	5.22±2.73	6.09±2.51	0.084
Aortic strain (%)	9.49±4.81	11.43±4.66	**0.033**
Aortic stiffness index (β)	2.95±0.57	2.75±0.48	**0.048**

A=ventricular filling velocities; E= Early ventricular filling velocities EF= Ejection fraction; LVEDD= Left ventricular end-diastolic diameter; LVESD= Left ventricular end- systolic diameter

Table 3.Tissue doppler results of study groups

	Patient (n=52)			
	Negative serum IgA-tTG (n=21)	**Positive serum** IgA-tTG **(n=31)**	**Controls (n=60)**	**P values**
Mitral annulus				
Sm velocity (cm/s)	6.52±1.89	6.29 ±1.62	7.15±1.65	0.020 [b]
Em velocity (cm/s)	10.90 ±2.40	10.55 ±2.33	12.58±2.55	<0.05 [a b]
Am velocity (cm/s)	4.95 ±1.59	4.97 ±1.37	5.7±1.29	<0.05 [a b]
Em/Am ratio	2.34±0.77	2.21±0.54	2.26±0.51	>0.05
Mitral ICT (ms)	74.33 ±9.61	73.00 ±8.12	65.73±12.30	0.005 [a b]
Mitral IRT (ms)	70.81 ±9.56	73.39 ±7.00	61.31±8.88	<0.001 [a b]
Mitral E/Em ratio	0.96 ±0.24	0.98 ±0.25	0.77±0.22	<0.001 [a b]
LV Tei index	0.63 ±0.11	0.66 ±0.11	0.47 ±0.09	<0.001 [a b]
Tricuspid annulus				
Sm velocity (cm/s)	8.48 ±2.37	9.45±2.04	10.16±2.1	0.003 [a]
Em velocity (cm/s)	11.57 ±1.94	11.29 ±1.86	13.03±2.42	0.001 [a b]
Am velocity (cm/s)	6.66±1.74	6.51±1.84	7.48±2.37	>0.05
Em/Am ratio	1.80±0.34	1.83±0.50	2.26±0.51	>0.05
Tricuspid ICT (ms)	73.95 ±10.89	74.64 ±8.67	63.80±12.79	<0.001 [a b]
Tricuspid IRT (ms)	73.95 ±11.25	79.61 ±10.20	60.22±10.72	<0.001 [a b]
E/Em ratio	0.76 ±0.17	0.72 ±0.18	0.63±0.14	0.002 [a b]
Rv Tei index	0.61±0.12	0.68 ±0.10	0.46±0.08	<0.001 [a b] 0.0027[c]

[a] Statistically significant difference between negative anti-tTg antibody and control groups; [b] Statistically significant difference between positive anti-tTg antibody and control groups.; [c] Statistically significant difference between positive anti-tTg antibody and negative anti-tTg antibody groups; (Am: late diastolic velocity; Em: early diastolic velocity; ICT: isovolumetric contraction time; IRT: isovolumetric relaxation time; Sm: peak systolic velocity; LV: Left ventricular; RV: right ventricular; IgA-tTG: IgA-tissue transglutaminase)

Table 4. The correlation between elasticity parameters and systolic and diastolic blood pressure in CD

	Stiffness index	**Distensibility**	**Strain (%)**
Systolic blood pressure	0.212	-0,314	-0.194
r	0.025	0.001	0.041
P			
Diastolic blood pressure			
r	0.193	-0.137	-0.318
P	0.042	0.151	0.001

DISCUSSION

In this study, it was found that patients with subclinical CD, especially in serum IgA-tTG antibody positive group, have increased SI and decreased aortic strain compared to controls. Moreover, these changes were found to be correlated with systolic and diastolic blood pressures. Although conventional echocardiography parameters were normal, LV and RV Tei indexes detected by TDI were significantly higher in children with CD than the control group. In addition, RV Tei index value was the highest in the group of IgA-tTG antibody positive.

Various types of cardiac involvement have been described in CD, and cardiovascular diseases are the main cause of mortality in this group of patients[17]. The frequency of autoimmune myocarditis and idiopathic dilate cardiomyopathy is increased in patients with CD due to the disordered immunological response [4]. In a study performed in patients with myocarditis, the presence of CD was found to be 4.4% with a prevalence 14 times higher than normal control group[4]. Another study showed that serum total carnitine levels decreased in CD-associated cardiomyopathic patients compared to isolated cardiomyopathic patients[18]. Because of this data, recent investigations have focused on noninvasive echocardiography methods that can detect subclinical myocarditis. In a small number of studies in children with CD, early cardiac

involvement has been shown to be detectable by TDI echocardiography [8, 19].

In our study, there was no significant cardiac dysfunction between patients and controls according to conventional echocardiography in accordance with the literature[8,19]. However, when 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, we reported significant prolongation in the IRT and ICT at the mitral annulus and at the tricuspid annulus in children with CD. Fathy et al.[8] showed cardiac dysfunction using TDI echocardiography in their study of 20 children with subclinical CD. In the same study, it was found that the left and right ventricular Tei index, which was first observed using TDI, was significantly higher in the patient group [8]. In our study, similarly, we found a significantly higher TDI-derived Tei index both in LV and RV in children with CD. Moreover, RV Tei index value was the highest in the group of serum IgA-tTG antibody positive. 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 RV Tei index in serum IgA-tTG antibody 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[10]. The relationship between the onset of atherosclerosis and inflammation and immune response has been demonstrated[20]. Autoimmune response which is considered as the most current hypothesis may cause atherosclerosis-related autoantigenesis leading to the activation of T cells [20]. The immunological response also occurs in CD, an autoimmune inflammatory disorder, leading to tissue destruction and the production of autoantibodies. A positive correlation between ischemic heart disease and non-specific inflammation and autoimmunity has been previously described [21].

A cohort study of a large group of patients with CD with mucosal inflammation of the small intestine showed an increased risk of ischemic heart disease irrespective of the histopathology of the small intestine [22]. However, the number of studies investigating cardiovascular risk factors in children with CD is limited. In a multicenter study enrolled with 114 children diagnosed as CD, 14% of patients had one or more traditional cardiovascular risk factors such as dyslipidemia or hypertension[23]. Preclinical atherosclerosis was assessed using pulse wave velocity and carotid artery intima-media thickness in pediatric CD and no difference was found between patients and controls.

Although atherosclerosis begins in childhood, cardiovascular complications develop rarely in this age. Gajulapalli et al. [24], showed in their cohort study that adult CD patients had a twofold increase in coronary artery disease prevalence independent of age. However, data on cardiovascular events that may occur in the pediatric population are very limited. For this reason, in this study, preclinical atherosclerosis was investigated using aortic elasticity parameters in subclinical pediatric celiac disease patients. Children with CD showed aortic SI increase and decreased aortic strain in our study. When two patient groups were investigated separately we determined that these findings were caused by the IgA-tTG antibody positive group. Moreover, these changes were found to be correlated with systolic and diastolic blood pressures. These results suggest that children with CD are under the risk of early atherosclerosis especially in IgA-tTG antibody positive group. Therefore, considering the increased arterial blood pressure by age, one may speculate that children with CD may develop atherosclerosis in their adulthood.

The most important limitation of this study is the lack of long-term follow-up data on the affect of gluten-free dietary in the cardiac involvement of the disease. The mean follow-up was 4.20 ± 2.12 years in our study and was similar in both patient groups. Another limitation is the low number of subjects enrolled in the study. However, the number of patients was similar to those used in other studies related to this disease. However, there is a need for large multicenter studies involving more patients with longer follow-up to confirm our findings of subclinical cardiac involvement in patients with CD.

In conclusion, our study showed that aortic elasticity parameters in children with subclinical CD are related to arterial pressure and may be used to determine increased prematurity atherosclerosis risk.

In these patients biventricular myocardial dysfunction coexists with decreased aortic elasticity properties. These results highlight the significance of early recognition of cardiovascular risk factors in children with CD and close follow-up for the patients especially in those with positive IgA-tTG antibodies.

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