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Evaluation of Aortic Elasticity in Children with Celiac Disease Compared with Controls

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Abstract

Background

Celiac disease (CD) is a lifelong, chronic and immune-mediated disorder. Recent studies have turned on a new light on the importance of inflammation in the pathogenesis of arterial stiffness. The aim of this study was to evaluate arterial stiffness in children with celiac disease compared with controls.

Materials and Methods: In this case-control study, fifty children aged from 3.5 to 18 year- old with celiac compared with 50 age and sex-matched controls. The study performed in Ali Asghar pediatric hospital in Zahedan city, Iran during the year 2019. Echocardiography, aortic elasticity, blood pressure, tissue transglutaminase IgA (tTG-IgA), and anthropomorphic parameters were measured. Arterial stiffness indices determined using 2D and Doppler echocardiography. Data were analyzed using SPSS software version 20.0.

Results: In all and CD children, 51% and 56% were girls, respectively. Systolic and diastolic blood pressure were lower in patients ($p<0.001$). Aortic diameter in diastole was lower in patients significantly ($p<0.001$). Aortic strain (<0.001), PSEM (<0.001), AD (<0.001), and ASI ($p<0.001$) were different between celiac patients and controls. Tissue transglutaminase IgA (tTG-IgA) was changed significantly with Marsh classification ($p<0.001$); tTG-IgA was correlated with strain ($r= 0.417$, $p=0.003$), and AD ($r= 0.282$, $p=0.047$) before age control when the trends did not change after age control for AD ($r=0.241$, $p=0.096$). LVMI was correlated with strain (r=-0309, $p=0.029$), PSEM ($r=0.322$, $p=0.023$), and AD ($r=0.326$, $p=0.021$) before controlling age when after age control this significant correlation omitted.

Conclusion

Concluded that aortic elastic risk is higher in celiac children when is free of modified marsh classification. Most of the aortic elastic parameters had significant correlation with changes of tTG-IgA antibody in children with celiac disease.

***Key Words**:* Aortic Elasticity, Celiac Disease, Children, Echocardiography.

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1- INTRODUCTION

Celiac disease (CD) is an autoimmune response to ingestion of gluten protein, which is found in wheat, rye, and barley grains, and results in both small intestinal manifestation of villous atrophy and systemic manifestations and the main treatment for the disease is a gluten-free diet (GFD) (1). CD prevalence varied from 0.3% in Germany to 2.4% in Finland. In which is higher 1.5 to 2 times in females than males and it influences around 0.6 to 1.0%, of total population between different regions of the world (2). Has been reported that, based population studies in Europe, India, South America, Australasia and the USA are indicate the variation from 0.33 and 1.06% in children (3). The reason for the recent increases in the number of reported cases is unclear (4).

However, it may be is at least due to changes in diagnostic practice (5). Inflammation associated with celiac disease may lead to an increased risk of problems on many organs and systems of the body. CD has already been linked to arrhythmias, or irregular heartbeats, and possible heart failure. Now, a new study has found that people with CD have almost a two-fold increased risk of coronary artery disease (CAD), compared to the general population (6). Cardiovascular diseases are the most widely recognized sickness, which needs restorative consideration exceptionally in children. One of the most significant noninvasive strategies is assessing aortic elastic parameters to recognize higher danger of future cardiovascular events (7). Aortic elastic parameters regularly are the aftereffect of incorporating cardiovascular hazard factors on the blood vessel divider over an extensive stretch of time. Estimating of aortic elastic parameters may open a window of opportunity to avert the event of cardiovascular infection even before first manifestations become characteristic, which is an important aspect of health care (8). Aortic elastic parameters are the consequence of regular maturing and natural aging that might be affected by numerous components of hereditary inclination and cardiovascular hazard factors (9). Aortic elastic parameters are early signs of structural and functional changes of the vessel wall and an independent predictor of cardiovascular disorders, which arise because of arteriosclerosis (8). Many studies have been conducted about the aortic elastic changes due to various diseases such as celiac (10), asthma (11), diabetes mellitus (12), end stage renal (13), and thalassemia (14). Has been reported that CD patients with abnormal homocysteine, erythrocyte sedimentation rate, C-reactive protein, and insulin levels but without cardiovascular risk factors are contributive to arterial stiffening (15). There is an increased risk of ischemic heart disease and higher cardiovascular mortality in CD despite the lack of traditional risk factors including blood pressure, body mass index, serum cholesterol, lipids, exercise, and smoking (6). Arterial functions are of great concern in CD. Measurements to quantify alterations are made using echocardiography and pulse wave velocity (15, 16). In untreated CD, aortic functions can deteriorate, and this deterioration is predictive of subclinical atherosclerosis and future cardiovascular events (16). Aortic strain and distensibility (aortic anatomy assessment) tend to be significantly lower, and the aortic stiffness index significantly higher, in untreated CD patients (10, 16). Regarding the subjects mentioned above, the study aimed to evaluate aortic stiffness changes in celiac children compared with controls.

2- MATERIALS AND METHODS

2-1. Study design

This case-control study was performed on 100 participants aged 3.5 to 18 years consisted of 50 healthy children

as controls and 50 children with CD as case group in pediatric cardiac center in collaboration with specific diseases center in Ali Asghar hospital, Zahedan city, Sistan and Baluchestan province, Iran, during the year 2019. Controls were chosen from those healthy children that referred to the clinics for routine check-up. Celiac disease diagnosed based on a combination of clinical findings and laboratory's tests (tTG-IgA) with a cut point of 20 and confirmed by intestinal biopsy (marsh classification). After considering the exclusion criteria and confirmation by intestinal biopsy were enrolled in the study. The Marsh Classification are stages through which a normal mucosa (Marsh 0) and pathological stages are included of Marsh I, II, III such that Marsh III into three subtype (a, b, c) has been defined.

2-2. Criteria

Healthy subjects were defined as without known chronical illness at the time of enrollment. The following exclusion criteria were used for both CD children and controls: age more than 18 years at entry, co-morbid disease or conditions such as diabetes mellitus, obesity, hypertension, dyslipidemia, systemic autoimmune disease, active infection, evidence of liver, renal and lung disease, smoking exposure, concurrent treatment with antihypertensive drugs, lipid-lowering drugs and positive family history for dyslipidemia and early coronary arterial disease.

2-3. Echocardiography measurements

Major proceedings on patients were checking medical history, physical examination, chest X-ray and echocardiography that was performed by one pediatric cardiologist. Echocardiography was performed on participants by the same pediatric cardiologist using My lab 60 with transducer 3, 8 (made in Italy). In order to achieve high precision in echocardiography findings, measurement was repeated for 3 cycles and the average was considered. Echocardiogram was performed on participants without them holding their breath.

Echocardiography findings by M-mode were: diastolic diameter of the aorta (Aod), systolic diameter of the aorta (Aos), left ventricular end diastolic dimension(LVDD), posterior wall dimension in diastole(PWD), interventricular septal dimension in Diastole(IVSD), interventricular septal dimension in systole(IVSS), RWT: Relative wall thickness(RWT) that defined as 2 times PWT divided by the LV diastolic diameter , Ejection fraction (EF), fractional shortening(FS), left ventricular mass (LVM) and left ventricular mass index (LVMI) were measured using conventional echocardiography of the left side and estimated from three cardiac cycles. LVMI was calculated by the following formula: LVM (g) = 0.8 (1.04 (LVDD + PWD + IVSD) ^{3} - LVDD ^{3}) + 0.6, and LVMI (g/m^2) = LVM / 2.7 (g/m^2). All the parameters in the above formula were measured in the M-mode view and in diastole and were utilized for left ventricular mass evaluation (15).

After routine echocardiographic investigation, ascending aorta were obtained from 3 cm above the aortic valve by the M-mode. Aortic diameters were calculated as the distance between the anterior and posterior wall inner edges of the aorta at systole and diastole. Aos was recorded when the aortic wall was fully open. Aod was recorded simultaneously when the QRS peak was seen on electrocardiographic (ECG) recordings. Measurements were taken during three consecutive pulses and the mean was calculated. Doppler tissue echocardiography (DTE) is another method that was performed from the apical four-chamber view and a 3 mm pulsed

Doppler sample volume was placed at the level of 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'. Left and right S': Systolic myocardial velocity above the baseline in mitral and tricuspid. Left and Right E': early diastolic myocardial relaxation velocity below the baseline in mitral and tricuspid. Left and Right A': myocardial velocity associated with atrial contraction in mitral and tricuspid (17).

2-4. Blood pressure (BP) measurement

Blood pressure (BP) levels were measured from the brachial artery at the level of the heart with a sphygmomanometer after resting for at least 5 min in the supine position. Three measurements, at least 2 min apart, were carried out, and the average of the closest two readings was recorded. A pressure drop rate of approximately 2 mm Hg/s was applied, and Korotkoff (sounds heard during measurement of blood pressure) phases I and V were used for systolic and diastolic BP levels, respectively. A cardiologist made all BP measurements. Pulse pressure (PP) was calculated as systolic minus diastolic BP.

2-5. Assessment of Aortic Elasticity

The systolic and diastolic ascending aortic diameters were recorded in M-mode under echocardiographic and electrocardiographic guidance approximately 3 cm above the aortic valve from parasternal long axis views. The systolic aortic diameter was measured at the time of maximum anterior motion of the aorta while the diastolic diameter was measured at the start of the QRS complex in electrocardiography. The following formulas were used to assess the aortic elasticity of the aorta (child sciences) (18).

Aortic strain (%) = (aortic SD [systolic diameter]-aortic DD [diastolic diameter]) x100/aortic DD

Aortic stiffness beta index=natural logarithm (systolic BP [blood pressure]/diastolic BP)/ ([aortic SD-aortic DD]/aortic DD).

Aortic distensability (cm2.dyne-1.10-6) = 2x ([aortic SD-aortic DD]/ aortic DD)/ (systolic BP-diastolic BP).

Pressure strain elastic modulus = (systolic BP–diastolic BP)/ ([aortic SD–aortic DD]/aortic DD).

Pulse pressure (mmHg) = SBP – DBP.

2-6. Anthropomorphic measurements

An experienced expert using standard equipment measured the participants' height and weight. Then, body mass index (BMI) was calculated according to the 2000 sex specific BMI-for-age growth charts of the Centers for Disease Control and Prevention. Participants' height was measured in the standing position with a balance using a scaled ruler and weight was calculated using a RASA scale factor with an error of 100 g (made in Iran). Then BMI was calculated as weight / height^2 (kg /m^2).

2-7. Ethical Approval

Consent form was obtained from the participants or their guardians after the study approval. The study was approved as a project proposed to the Children and Adolescent Health Research Center by the Ethics Committee of Zahedan University of Medical Sciences, Zahedan, Iran (ID number: 9359).

2-8. Statistical Analysis

Data were analyzed using SPSS software version 20.0 (SPSS Inc., Chicago, IL,

USA). Kolmogorov-Smirnov test was used to assess normality of continuous variables. Student's t-test was used to compare mean values of quantitative variables with normal distribution while Mann-Whitney U test was used to compare quantitative variables with skewed distribution. In correlation analyses, Pearson correlation coefficient was used for parametric variables while Spearmen test was used for non-parametric variables. P-value < 0.05 was considered as statistically significant

3- RESULTS

The variables' distribution of Aos (p=0.089), Aod (p=0.165), IVSS (p=0.161), IVDS (p= 0.200), and right E'(p=0.190) were normal in participants, when this pattern for patients was for variables of age (p=0.065), Height (p=0.200), IVSD (p=0.200), LVDD (p=0.200), PWD (p=0.200), IVDS (p=0.064), PWS (p=0.200), ASW (p=0.200), and AS (p=0.200) (**Table. 1**). From the participants, 51% were girls in which distributed in case and controls of 56% and 46%, respectively. This distribution of gender in case and controls was matched (Chi-square= 1.00, and p=0.317). Means' age of celiac patients and controls were 8.78±3.04 and 9.16±1.48 years old, respectively (p=0.504). Patients' height and weight were lower than controls significantly (p<0. 05).

Table-1: Kolmogorov-Smirnov test for normality of the variables for all participants (100 children) and Celiac diseases (50 children).

All Participants					Celiac Patients			
Variables	Mean	SD	K.S	P value	Mean	SD	K.S	P value
Age	8.97	2.38	0.125	0.001	8.78	3.04	0.121	0.065
Weight	28.49	13.28	0.172	<0.001	24.66	10.40	0.167	0.001
Height	125.97	15.57	0.15	<0.001	122.00	20.16	0.108	0.2
BMI	16.87	2.38	0.080	0.120	15.99	2.78	0.195	<0.001
SBP	95.36	11.22	0.26	<0.001	87.30	9.70	0.254	<0.001
DBP	62.05	9.69	0.206	<0.001	55.40	8.01	0.297	<0.001
Aortic diameter in diastole	1.99	0.30	0.083	0.089	1.97	0.29	0.141	0.015
Aortic diameter in systole	1.77	0.31	0.076	0.165	1.66	0.30	0.143	0.012
IVSD	0.63	0.12	0.097	0.022	0.59	0.13	0.086	0.2
LVDD	3.59	0.61	0.098	0.019	3.43	0.47	0.092	0.2
PWD	0.33	0.07	0.104	0.01	0.30	0.07	0.098	0.2
IVSS	0.76	0.15	0.076	0.161	0.70	0.12	0.161	0.002
LVDS	2.02	0.36	0.054	0.2	1.98	0.41	0.121	0.064
PWS	0.33	0.07	0.104	0.01	0.30	0.07	0.098	0.2
EF	0.76	0.06	0.144	<0.001	0.74	0.06	0.162	0.002
FS	0.44	0.05	0.093	0.033	0.41	0.05	0.148	0.008
Left S'	0.08	0.01	0.176	<0.001	0.08	0.01	0.144	0.011
Left E'	0.15	0.03	0.115	0.002	0.14	0.04	0.159	0.003
Left A'	0.07	0.02	0.162	<0.001	0.07	0.02	0.149	0.007
Right S'	0.09	0.02	0.128	<0.001	0.09	0.02	0.18	<0.001
Right E'	0.14	0.03	0.075	0.19	0.13	0.03	0.138	0.018
Right A'	0.07	0.02	0.194	<0.001	0.07	0.02	0.285	<0.001
RWT	0.19	0.12	0.305	<0.001	0.18	0.05	0.204	0.048
LVMI	16.41	7.07	0.103	0.011	14.03	6.51	0.209	<0.001
TTG	-	-	-	-	141.88	82.35	0.287	<0.001
Aortic Strain (%)	13.37	8.49	0.112	0.003	19.51	7.31	0.104	0.200
PP (mm/Hg)	33.31	7.28	0.225	<0.001	31.90	7.95	0.234	<0.001

PSEM (kPa)	423.63	397.32	0.184	<0.001	193.20	105.20	0.13	0.035
AD ($cm^2.dyne^{-1}.10^{-6}$)	0.01	0.01	0.144	<0.001	0.02	0.01	0.189	<0.001
ASI	5.29	4.83	0.202	<0.001	2.76	1.42	0.125	0.05

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, Aod: Aortic diameter in diastole, Aos: Aortic diameter in Systole, IVSD: Interventricular septal dimension in Diastole, LVDD: Left ventricular end diastolic dimension, PWD: Posterior wall dimension in diastole, IVSS: Interventricular septal dimension in systole, LVDS: Left ventricular end systolic dimension, PWS: Posterior wall dimension in systole, EF: Ejection Fraction, FS: Fractional Shortening, S': Systolic myocardial velocity, E': Early diastolic myocardial relaxation velocity, A': Late diastolic myocardial velocity, ASI: Aortic Stiffness Index, PP: Pulse pressure, AD: Aortic distensibility, PSEM: Pressure strain elastic modulus, BMI: Body mass index, RWT: Relative wall thickness, LVMI: Left ventricular mass index, SD: Standard deviation, K.S: Kolmogorov–Smirnov test.

From the **Table. 2** revealed that systolic and diastolic blood pressure were lower in patients than control significantly (p<0.001). Aortic diameter in systole was higher in controls, but not significantly, when aortic diameter in diastole was lower in patients significantly (p<0.001). Amongst M mode echocardiography findings, IVSD (p=0.008), LVDD (p<0.001), PWD (p<0.001), IVSS (p<0.001), PWS (p<0.001), EF (P<0.001), ES (P<0.001) were lower in patients significantly. Amongst Doppler tissue findings, left S' (p=0.791), Left A' (p=0.146), right S' (P=0.819) were not significant when left E' (p=0.014), right E' (<0.001), and right A' (p=0.019) were significant in patients and controls comparison. Aortic stiffness parameters of Strain (p<0.001), PSEM (p<0.001), and AD (p<0.001). ASI (p<0.001) were different significantly between celiac patients and controls when PP (p=0.073) not significant.

Table-2: Anthropomorphic, blood pressure, echocardiography and aortic elasticity findings comparisons between case and controls.

Variables	Group	Mean	SD	Mean Rank	Sum of Ranks	Test value	P-value	Variables	Mean	SD	Mean Rank	Sum of Ranks	Test value	P-value
SBP	Case	87.3	9.7	30.22	1511	236	0	LVMI	14.0298	6.50960	38.89	1944.50	669.5	<0.001
	Control	103.42	5.26	70.78	3539				18.7877	6.86749	62.11	3105.50		
DBP	Case	55.4	8.01	30.4	1520	245	0	Left S'	0.08	0.01	51.25	2562.5	1212.5	0.791
	Control	68.7	5.96	70.6	3530				0.08	0.01	49.75	2487.5		
Aortic diameter in diastole	Case	1.97	0.29	-	-	-0.75	0.547	Left E'	0.14	0.04	43.47	2173.5	898.5	0.014
	Control	2.02	0.3	-	-				0.15	0.02	57.53	2876.5		
Aortic diameter in systol	Case	1.66	0.3	-	-	-3.71	<0.001	Left A'	0.07	0.02	54.64	2732	1043	0.146
	Control	1.88	0.29	-	-				0.07	0.01	46.36	2318		
IVSD	Case	0.59	0.13	42.84	2142	867	0.008	Right S'	0.09	0.02	49.84	2492	1217	0.819
	Control	0.66	0.11	58.16	2908				0.09	0.02	51.16	2558		
LVDD	Case	3.43	0.47	39.88	1994	719	<0.001	Right E'	0.13	0.03	-	-	-4.975	<0.001
	Control	3.76	0.68	61.12	3056				0.15	0.02	-	-		
PWD	Case	0.3	0.07	40.08	2004	729	<0.001	Right A'	0.07	0.02	43.74	2187	912	0.019
	Control	0.35	0.05	60.92	3046				0.07	0.02	57.26	2863		
IVSS	Case	0.7	0.12	-	-	-4.293	<0.001	Aortic Strain (%)	19.51	7.31	72.82	3641	134	<0.001
	Control	0.82	0.16	-	-				7.24	3.94	28.18	1409		
LVDS	Case	1.98	0.41	-	-	-1.056	0.294	PP (mm/Hg)	31.9	7.95	45.54	2277	1002	0.073
	Control	2.06	0.32	-	-				34.72	6.31	55.46	2773		
PWS	Case	0.3	0.07	40.08	2004	729	<0.001	PSEM	1.93	1.05	28.4	1420	145	<0.001

	Control	0.35	0.05	60.92	3046			(kpa)	6.54	4.46	72.6	3630		
EF	Case	0.74	0.06	39.41	1970.5	695.5	<0.001	AD ($cm^2.dyne^{-1}.10^{-6}$)	0.02	0.01	71.65	3582.5	192.5	<0.001
	Control	0.78	0.05	61.59	3079.5				0.01	0	29.35	1467.5		
FS	Case	0.41	0.05	36.06	1803	528	<0.001	ASI	2.76	1.42	30.56	1528	253	<0.001
	Control	0.46	0.04	64.94	3247				7.82	5.67	70.44	3522		
RWT	Case	.1789	.04439	46.59	2329.50	1054.5	0.178	BMI	15.99	2.78	-	-	-3.987	<0.001
	Control	.2096	.16783	54.41	2720.50				17.75	1.44	-	-		

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, IVSD: Interventricular septal dimension in Diastole, PWD: Posterior wall dimension in diastole, IVSS: Interventricular septal dimension in systole, PWS: Posterior wall dimension in systole, S': Systolic myocardial velocity, E': Early diastolic myocardial relaxation velocity, A': Late diastolic myocardial velocity, RWT: Relative wall thickness, LVMI: Left ventricular mass index, ASI: Aortic Stiffness Index, PP: Pulse pressure, AD: Aortic distensibility, PSEM: Pressure strain elastic modulus, BMI: Body mass index, SD: Standard deviation.

Tissue Transglutaminase Antibodies (tTG-IgA) ($p<0.001$), AoS ($p=0.020$), PWS ($p=0.001$), LVMI ($p=0.004$), IVSS ($p=0.001$), IVSD ($p=0.001$), PWD ($p=0.001$), and RWT ($p=0.001$) were changed significantly with Marsh classification changes (**Table.3**). **Table.4** shows pairwise comparisons of significant variables. In pairwise comparison, tTG-IgA antibody changed based on Marsh classification due to all pairs except Marsh IIIB and Marsh IIIC pair. AoS changed based on Marsh classification due to pairs of Marsh IIIA and Marsh IIIB and, Marsh IIIA and Marsh IIIC. IVSD changed from Marsh IIIA to Marsh IIIB and from Marsh IIIA to Marsh IIIC. PWD changed from Marsh IIIA to Marsh IIIB and from Marsh IIIB to Marsh IIIC. PWS changed from Marsh IIIA to Marsh IIIB. IVSS changed from Marsh IIIA to IIIB and IIIA to IIIC. RWT changed from Marsh IIIA to Marsh IIIB and from Marsh IIIB to Marsh IIIC. LVMI changed from Marsh IIIA to Marsh IIIB and from Marsh IIIA to Marsh IIIC.

Table-3: Tissue transglutaminase IgA (tTG-IgA), blood pressure, echocardiography and aortic elasticity findings comparisons between Marsh Classification in Children with celiac (50 children).

Variables	MARSH	Mean Rank	MEAn	SD	X^2	P-value	Variables	Mean rank	Mean	SD	X^2	P-value
tTG-IgA	MAR2	10.06	84.38	20.08	30	<0.001	LVMI	24.13	13.94	6.57	13.51231	0.004
	MAR3A	19.5	104.09	13.75				33.22	17.19	6.86		
	MAR3B	39.5	225.83	114.02				17.58	10.70	4.29		
	MAR3C	38.86	187.86	62.71				15.29	9.47	2.23		
SBP	MAR2	15.38	80	7.56	5.28	0.071	IVSS	25.63	0.73	0.16	14.31	0.001
	MAR3A	28.54	89.13	9.37				34.48	0.77	0.1		
	MAR3B	26.29	88.33	10.3				14.42	0.61	0.07		
	MAR3C	25.71	87.86	9.94				14.86	0.62	0.04		
DBP	MAR2	18.5	51.25	8.35	2.97	0.226	Right E'	22.38	0.12	0.02	0.22	0.897
	MAR3A	28.35	56.52	9.59				24.48	0.13	0.02		
	MAR3B	23.5	55	5.22				25.25	0.13	0.03		
	MAR3C	27.57	57.14	4.88				32.86	0.15	0.03		
AoD	MAR2	23.63	1.93	0.32	7.87	0.02	Right A'	27	0.07	0.03	1.09	0.579
	MAR3A	32.65	2.1	0.3				25.43	0.06	0.02		
	MAR3B	18.5	1.86	0.24				21.21	0.06	0.03		
	MAR3C	16.14	1.79	0.16				31.36	0.07	0.02		

LVDS	MAR2	21.5	1.91	0.21	3.4	0.183	Left S'	31.75	0.09	0.01	2.51	0.285
	MAR3A	30.48	2.1	0.47				22.83	0.08	0.01		
	MAR3B	26.33	2.02	0.26				23.88	0.08	0.01		
	MAR3C	12.29	1.57	0.33				29.93	0.09	0.02		
PWS	MAR2	21.75	0.28	0.08	14.89	0.001	Left E'	28.31	0.15	0.05	0.66	0.721
	MAR3A	33	0.34	0.06				23.59	0.14	0.04		
	MAR3B	12.88	0.25	0.06				25.17	0.14	0.04		
	MAR3C	26.79	0.3	0.04				29.14	0.14	0.01		
EF	MAR2	33.69	0.77	0.04	5.11	0.078	Left A'	30.75	0.08	0.02	1.99	0.37
	MAR3A	21.09	0.72	0.06				22.2	0.07	0.02		
	MAR3B	22.17	0.72	0.05				25.75	0.07	0.02		
	MAR3C	36.36	0.79	0.05				29.93	0.08	0.02		
FS	MAR2	32.44	0.43	0.03	3.78	0.151	Right S'	30.31	0.09	0.02	2.43	0.297
	MAR3A	22.8	0.4	0.05				24.46	0.09	0.02		
	MAR3B	21.29	0.4	0.04				20.08	0.08	0.02		
	MAR3C	33.64	0.44	0.04				32.71	0.1	0.02		
AoS	MAR2	24.81	1.66	0.36	5.8	0.055	Strain	22.38	17.91	7.88	1.43	0.489
	MAR3A	31.91	1.78	0.29				23.22	18.29	6.1		
	MAR3B	20.58	1.56	0.28				28.42	20.14	6.3		
	MAR3C	13.64	1.45	0.15				31.57	24.24	10.92		
IVSD	MAR2	24.06	0.59	0.17	13.06	0.001	PP	19.88	28.75	3.54	1.74	0.419
	MAR3A	34.11	0.66	0.1				26.67	32.61	8.51		
	MAR3B	13.54	0.5	0.11				27.79	33.33	8.88		
	MAR3C	19.36	0.53	0.05				24.14	30.71	8.38		
LVDD	MAR2	27.44	3.47	0.38	2.15	0.341	PSEM	26.63	194.23	95.39	1.16	0.559
	MAR3A	29.96	3.59	0.51				28.3	201.2	85.77		
	MAR3B	23.67	3.37	0.2				22.92	199.84	153.62		
	MAR3C	11.79	2.96	0.46				19.43	154.37	86.2		
PWD	MAR2	21.75	0.28	0.08	14.89	0.001	AD	23.63	0.02	0.01	0.16	0.925
	MAR3A	33	0.34	0.06				25.89	0.02	0.01		
	MAR3B	12.88	0.25	0.06				25.33	0.02	0.01		
	MAR3C	26.79	0.3	0.04				26.64	0.02	0.01		
RWT	MAR2	18.56	.16	.03	17.209	0.001	ASI	29.25	3.02	1.52	1.06	0.587
	MAR3A	31.87	.19	.03				27.26	2.85	1.28		
	MAR3B	13.08	.15	.02				23.17	2.74	1.77		
	MAR3C	33.79	.21	.07				19.43	2.19	1.25		
BMI	MAR2	26.25	15.7483	1.72392	7.422	0.060						
	MAR3A	28.83	16.1319	2.01025								
	MAR3B	26.58	16.9467	4.53848								
	MAR3C	11.86	14.1298	1.11915								

tTG-IgA: Tissue transglutaminase IgA , SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, IVSD: Interventricular septal dimension in Diastole, PWD: Posterior wall dimension in diastole, IVSS: Interventricular septal dimension in systole, PWS: Posterior wall dimension in systole, S': Systolic myocardial velocity, E': Early diastolic myocardial relaxation velocity, A': Late diastolic myocardial velocity, RWT: Relative wall thickness, LVMI: Left ventricular mass index, ASI: Aortic Stiffness Index, PP: Pulse pressure, AD: Aortic distensibility, PSEM: Pressure strain elastic modulus, BMI: Body mass index, X^2: Chi-square test.

Table-4: Follow up test for significant variables' changes due to Modified Marsh Classification in celiac disease children, n=50.

Variables	Groups	Groups	P value	Variables	P-value
tTG-IgA	Marsh II	Marsh IIIA	0.013	PWS	0.107
		Marsh IIIB	<0.001		0.590
		Marsh IIIC	0..001		0.921
	Marsh IIIA	Marsh IIIA	<0.001		0.000
		Marsh IIIB	<0.001		0.475
	Marsh III**B**	Marsh IIIC	0.482		0.241
AoD	Marsh II	Marsh IIIA	0.203	IVSS	0.275
		Marsh IIIB	0.624		0.208
		Marsh IIIC	0.463		0.336
	Marsh IIIA	Marsh IIIA	0.004		<0.001
		Marsh IIIB	0.006		<0.001
	Marsh III**B**	Marsh IIIC	0.773		0.837
IVSD	Marsh II	Marsh IIIA	0.415	RWT	0.016
		Marsh IIIB	0.298		0.343
		Marsh IIIC	0.752		0.072
	Marsh IIIA	Marsh IIIA	0.001		<0.001
		Marsh IIIB	0.049		0.484
	Marsh III**B**	Marsh IIIC	0.925		<0.001
PWD	Marsh II	Marsh IIIA	0.143	LVMI	0.339
		Marsh IIIB	0.521		0.851
		Marsh IIIC	0.536		0.397
	Marsh IIIA	Marsh IIIA	<0.001		0.001
		Marsh IIIB	0.245		0.001
	Marsh III**B**	Marsh IIIC	0.022		0.902

tTG-IgA: Tissue transglutaminase IgA , AoD: Aortic diameter in diastole, IVSD: Interventricular septal dimension in Diastole, PWD: Posterior wall dimension in diastole, PWS: Posterior wall dimension in systole, IVSS: interventricular septal dimension in systole, RWT: Relative wall thickness, LVMI: Left ventricular mass index.

Table. 5 shows the correlation of aortic stiffness parameters with other variables in the study before and after age control. From the table observed that tTG-IgA antibody was correlated with Strain and AD before age control when the correlation with AD changed after age control. For systolic blood pressure, the same trends occurred for ASI, when the correlation maintained after age controls for PP, PSEM and AD. Diastolic blood pleasure was only correlated with ASI when after age control showed a correlation with all aortic stiffness parameters except aortic strain. Aortic diameter in systole had correlation with all

stiffness parameters except AD. When age controlled, the results showed correlation with none of stiffness parameters. Aortic diameter in diastole had correlation with all stiffness parameters. When age controlled, the results showed correlation with stiffness parameters of PSEM and ASI. LVMI had correlation with Strain, PSEM and ASI when these correlations omitted after age control.

Table-5: Tissue transglutaminase IgA antibody, BMI, echocardiography correlation with aortic elasticity findings in children with celiac (50 children) before and after controlling Age.

Variables	Statistics	Before controlling age					After controlling age				
		Strain	PP	PSEM	AD	ASI	Strain	PP	PSEM	AD	ASI
Celiac	r	-0.726	0.195	0.583	-0.669	.0526	-0.769	0.184	0.582	-0.67	0.524
	P-value	<0.001	0.052	<0.001	<0.001	<0.001	<0.001	0.068	<0.001	<0.001	<0.001
tTG-IgA	r	0.417	-0.151	-0.248	0.282	-0.270	0.382	-0.108	-0.155	0.241	-0.191
	P-value	0.003	0.295	0.083	0.047	0.058	0.007	0.46	0.286	0.096	0.190
BMI	r	-0.424	0.289	0.301	-0.373	0.291	-0.242	0.232	0.215	-0.305	0.200
	P-value	<0.001	0.004	0.002	<0.001	0.003	0.016	0.021	0.033	0.002	0.047
IVSD	r	-0.227	0.120	0.311	0.068	0.313	0.268	-0.028	-0.12	0.297	-0.047
	P-value	0.114	0.406	0.028	0.639	0.027	0.063	0.848	0.413	0.038	0.750
LVDD	r	-0.399	0.041	0.303	-0.04	0.298	0.069	-0.164	-0.227	0.198	-0.144
	P-value	0.004	0.775	0.032	0.781	0.035	0.637	0.261	0.116	0.173	0.324
PWD	r	-0.171	0.149	0.275	0.005	0.273	0.110	0.065	0.042	0.121	0.073
	P-value	0.235	0.302	0.054	0.970	0.055	0.452	0.656	0.775	0.406	0.620
IVSS	r	-0.185	0.047	0.188	0.131	0.208	0.254	-0.098	-0.24	0.338	-0.142
	P-value	0.198	0.748	0.191	0.365	0.147	0.079	0.505	0.097	0.018	0.329
LVDS	r	-0.282	-0.087	0.200	0.077	0.169	0.104	-0.261	-0.223	0.271	-0.199
	P-value	0.047	0.548	0.164	0.597	0.241	0.478	0.071	0.124	0.059	0.170
PWS	r	-0.171	0.149	0.275	0.005	0.273	0.110	0.065	0.042	0.121	0.073
	P-value	0.235	0.302	0.054	0.97	0.055	0.452	0.656	0.775	0.406	0.620
EF	r	-0.018	0.318	0.240	-0.251	0.247	-0.048	0.335	0.337	-0.269	0.322
	P-value	0.901	0.024	0.094	0.079	0.083	0.741	0.019	0.018	0.062	0.024
FS	r	-0.083	0.417	0.290	-0.319	0.290	-0.026	0.408	0.298	-0.305	0.287
	P-value	0.566	0.003	0.041	0.024	0.041	0.86	0.004	0.037	0.033	0.046
Left S’	r	0.16	0.173	0.099	-0.067	0.08	0.093	0.214	0.248	-0.11	0.196
	P-value	0.267	0.229	0.496	0.642	0.583	0.526	0.139	0.086	0.453	0.177
Left E’	r	0.047	-0.005	-0.001	-0.093	0.002	-0.263	0.088	0.32	-0.211	0.271
	P-value	0.747	0.973	0.995	0.52	0.991	0.068	0.547	0.025	0.145	0.06
Left A’	r	0.206	0.074	-0.047	-0.053	-0.105	-0.042	0.177	0.26	-0.168	0.135
	P-value	0.151	0.607	0.744	0.713	0.469	0.774	0.224	0.072	0.248	0.357
Right S’	r	0.116	0.184	0.041	-0.123	0.043	-0.008	0.239	0.216	-0.184	0.188
	P-value	0.42	0.202	0.778	0.394	0.766	0.954	0.098	0.137	0.206	0.195
Right E’	r	0.275	-0.112	-0.214	0.160	-0.215	0.154	-0.057	-0.073	0.100	-0.092
	P-value	0.053	0.438	0.136	0.267	0.133	0.29	0.699	0.619	0.495	0.530
Right A’	r	0.253	0.241	-0.023	-0.033	-0.038	0.105	0.326	0.205	-0.114	0.149
	P-value	0.077	0.092	0.876	0.822	0.795	0.473	0.022	0.158	0.436	0.308
RWT	r	0.144	0.038	0.021	0.141	0.014	0.133	0.055	0.084	0.128	0.064
	P-value	0.318	0.795	0.886	0.327	0.923	0.363	0.706	0.567	0.379	0.660
LVMI	r	-0.309	0.113	0.322	0.020	0.326	0.224	-0.063	-0.189	0.280	-0.094
	P-value	0.029	0.434	0.023	0.888	0.021	0.123	0.669	0.193	0.051	0.522

tTG-IgA: Tissue transglutaminase IgA , SBP: Systolic Blood Pressure, DBP : Diastolic Blood Pressure, Aod: Aortic diameter in diastole, Aos: Aortic diameter in Systole, IVSD: Interventricular septal dimension in Diastole, LVDD: Left ventricular end diastolic dimension, PWD: Posterior wall dimension in diastole, IVSS: Interventricular septal dimension in systole, LVDS: Left ventricular end systolic dimension, PWS: Posterior wall dimension in systole, EF: Ejection Fraction, FS: Fractional Shortening, S’: Systolic myocardial velocity, E’: Early diastolic myocardial relaxation velocity, A’: Late diastolic myocardial velocity, ASI: Aortic Stiffness Index, PP: pulse pressure, AD: Aortic distensibility, PSEM: Pressure strain elastic modulus, BMI: Body mass index, RWT: Relative wall thickness, LVMI: Left ventricular mass index, r: Pearson correlation coefficient.

4- DISCUSSION

The present study aimed to evaluate aortic stiffness changes in celiac children compared with controls in 3.5-18 years children in Ali Asghar hospital, Zahedan city, Sistan and Baluchestan province, Iran, during the year 2019. From the study resulted that systolic, diastolic blood pressure, aortic diameter in systole and diastole were low in celiac children. Most of the echocardiography and Doppler tissue findings were different between celiac and healthy children. Some of them are; IVSD, LVDD, PWD, IVSS1), PWS, EF, FS, left E', right E') and right A' that were lower in patients significantly. tTG-IgA antibody, AoS, PWS, LVMI, IVSS, IVSD, PWD, and RWT, were changed significantly with Marsh classification changes. Celiac disease is predominantly a disease of the small intestine that develops in genetically susceptible individuals after dietary exposure to grains containing gluten. Ingestion of gluten results in inflammation of the intestinal mucosa along with hyperplasia of the crypts and atrophy of the villi of the small intestine.

The inflammatory response is believed to be mediated by immune mechanisms. Classical findings of CD usually begin at 1–3 years of life. Toddlers and young children classically present with chronic diarrhea, vomiting, poor appetite, abdominal distension, abdominal pain, irritability, and failure to thrive after the introduction of gluten in the diet (19). Other manifestations include osteomalacia, coagulopathy, and peripheral neuropathy. A gluten-free diet usually results in complete resolution of the symptoms and correction of the metabolic abnormalities. From the study resulted that systolic, diastolic blood pressure, aortic diameter in systole and diastole were low in celiac children. Most of the echocardiography and Doppler tissue findings were different between celiac and healthy children. Some of them are; IVSD, LVDD, PWD, IVSS1), PWS, EF, FS, left E', right E') and right A' that were lower in patients significantly. tTG-IgA antibody, AoS, PWS, LVMI, IVSS, IVSD, PWD, and RWT, were changed significantly with Marsh classification changes. In Demir et al.'s study (20) resulted that celiac patients had a significant correlation between PWV and age, weight, height, body mass index, and systolic and diastolic blood pressure. Sari et al. (16), and Akin et al. (21) utilized conventional echocardiography to evaluate cardiovascular findings in celiac and healthy children. Both studies found that finding of EF was not significant, which is dissimilar with the present study. Akin et al. (21) also found that left E' was significantly similar to the present study. Noori et al. (17, 22) in a study to assess Doppler tissue echocardiography and electrocardiography in Children with Celiac concluded that the finding of left and right S', left A' were higher in celiac children significantly, when some parameters of left E', left A', EF, FS and LVMI were similar between the groups of patients and controls.

Fathy et al. (23) showed that left heart functions by DTI such as left E' and left S' were lower in celiac children when left A' did not changed from celiac to healthy children. Considering the right DTI parameters such as right E', right S' and right A', they found similar pattern in those in left. Karpuz et al. (24), found that conventional parameters of EF and FS were similar in celiac and healthy children. Karpuz classified celiac children in two groups of positive anti-tTg antibody and negative anti tTg antibody groups; and compared them with healthy children. They resulted that left S' was higher significantly in healthy children compared to only positive anti-tTg antibody, left E' and left A' had similar

pattern in case on positive anti-tTg antibody as well as negative anti-tTg antibody.in the case of right side of heart, S' was higher in healthy children compared to groups of celiac children with negative anti-tTg antibody, E' was higher in healthy children compared with both groups of celiac children. Peak E' velocity in right did not changed in all groups of the study. Bayar et al. (10) resulted that patients with CD did not have any differences in the conventional echocardiographic parameters compared to the healthy individuals. But found that Systolic and diastolic blood pleasure were higher in celiac and healthy children respectively. Sari et al. (16) conducted a study to evaluate the changes of aortic function in patients with celiac disease. The degree of aortic strain and aortic distensibility was significantly smaller in CD patients; but the ASI was significantly higher in CD patients.

Finally, they found that age and celiac disease were correlated both with aortic strain, and with aortic distensibility, celiac disease was the only parameter that correlated with ASI. After multivariate analysis, celiac disease was the sole independent factor for aortic strain, aortic distensibility, and ASI. Bayar et al. (10) resulted that patients in the CD group had an increased aortic stiffness beta index, increased pressure strain elastic modulus, decreased aortic distensibility, and similar aortic strain compared to the control group. In multivariate linear regression Bayar et al. (10) found that age had significant effect on all stiffness parameters except ASI such that the effect on AS and AD was negative. Karpuz et al. (24) analyzed aortic elastic parameters of AD, AS and ASI and resulted that AD was similar between celiac and healthy children when AS and ASI were higher in children with celiac significantly. From the present study revealed that Aortic stiffness parameters of strain and Aortic distensibility were higher in celiac children when Aortic stiffness index (ASI) and Pressure strain elastic modulus (PSEM) were lower. tTG-IgA antibody was correlated with Aortic strain and AD before controlling age when the correlation with AD changed after age control. Aortic diameter in systole had correlation with all stiffness parameters except AD. When age controlled, the results showed correlation with none of stiffness parameters. Aortic diameter in diastole had correlation with all stiffness parameters. When age controlled, the results showed correlation with stiffness parameters of PSEM and ASI.

LVMI had correlation with Aortic strain, PSEM and ASI when these correlations omitted after age control. From the study resulted that BMI had negative and significant correlation with strain and AD when with other parameters had positive and significant correlation before controlling age. Same pattern observed for these correlations after controlling age with a higher value of significance. The specific antibody tests for CD are the initial tools that are used to identify individuals in need of further investigation to diagnose or exclude CD. Systematic review comparing the endomysial (EMA), and tissue transglutaminase (tTG) antibodies concluded that human recombinant tTG-IgA antibody is the preferred test for screening asymptomatic people and for excluding celiac disease in symptomatic individuals (24).

Significant association of high anti-tTG titer and histological changes in CD had been reported in many retrospective studies of CD (26, 27). Donaldson et al. showed that all their pediatric patients with anti-tTG titer ≥ 100 U/mL had Marsh III histopathology of CD (28). In Demir et al.'s study (20), reported that histopathological analysis was compatible with Marsh classification such that they found the number of celiac patients was

high in the Marsh III type c CD. Hawamdeh et al. (29), carried out a study to assess an association between tTG-IgA Antibody Titer and modified Marsh classification in Children with Celiac Disease. They resulted that among the children with celiac 81.5% had positive modified Marsh classification of CD while 18.5% were normal. From those with positive modified Marsh classification 74.2% had Marsh III, and 25.8% had Marsh I or II. From the children with celiac, 63% had an anti-tTG titer ≥ 180 U/mL, and 37% had a titer less than 180 U/mL. To assessment of association of anti-tTG titer with the modified Marsh classification they found that from those with anti tTG ≥ 180, 78.4% had Marsh III, 15.7% had Marsh I or Marsh II, and only 5.9% had normal duodenal biopsies as Marsh 0.

From those with anti-tTG < 180 U/mL, 40% had normal duodenal biopsies, and 60% had histological changes of celiac disease; half of them had Marsh III. Obviously has been presented a significant association between anti-tTG Titers and the degree of duodenal damage, and this association is stronger between anti-tTG titer ≥ 180 U/mL and Marsh III. Rahmati et al. (30), found that while there was no significant differences in tTG levels in patients with villous atrophy, mean tTG titers were significantly lower in Marsh I and II grades than the other three grades. Paul et al. (31) attempted to find correlation tTG antibody levels and modified Marsh classification in celiac disease. They concluded an increasing tTG antibody levels from grade 0 to grade III. The present study attempted to assess the changes of aortic stiffness parameters, changes of echocardiography findings and tTG-IgA antibody levels. From the study revealed that tTG-IgA antibody levels were changed based on marsh with a significant increase by marsh grading. tTG-IgA antibody mean had an increase from Marsh II to Marsh IIIB and decrease then to Marsh IIIC. In pairwise comparison, significant observed in all pair groups except Marsh IIIB and Marsh IIIC. These results are comparable with the recent results. From the present study also revealed that none of aortic elastic parameters did not change with modified Marsh classification, while, some of conventional parameters changed such as IVSD, AoS, PWD, PWS, IVSS, RWT and LV. In this regards, Fathy et al. (23) resulted that the modified Marsh classification of the histologic findings in CD patients were significantly positively correlated with the RV MPI. Although the LV MPI seems to be more affected in patients with more severe histologic findings according to modified Marsh classification, this relation did not reach statistical significance.

On the other hand, FS was not correlated with the modified Marsh classification. The present study considered some of cardiac parameters and was similar in results in FS that found non-significant changes. Aging leads to a multitude of changes in the cardiovascular system including increased vascular stiffness. In fact, age related increases in blood pressure are mainly attributable to an increase in systolic blood pressure while maintaining or having a slight decrease in a diastolic blood pressure. This leads to a widening in pulse pressure (difference between systolic and diastolic blood pressure). Systolic hypertension is so closely related to aging that people 65 years of age have a 90% chance of developing hypertension in their lifetime. Age and blood pressure were responsible for 34% of the change in aortic stiffness. All other factors were attributed to 4% of the change (32).Aortic stiffness has a strong effect on cardiovascular prognosis. This association can be explained by three primary mechanisms (33). First, increased aortic stiffness may contribute to

atherosclerotic progression to other arteries such as the coronary and carotid arteries. Second, in addition to Aortic stiffness, SBP and pressure on vital organs is increased, contributing to the risk of atherosclerotic complications. Last, endothelial dysfunction can lead to AS and atherosclerotic progression. Therefore, aortic stiffness parameters play important role in cardiovascular events (34).

4-1. Study Limitations

The main limitation of the study was low sample size for both groups in the study lack of proper contribution by the children's parents especially in controls.

5- CONCLUSION

From the study concluded that children with CD are more at risk with aortic stiffness than healthy ones. In children with CD, none of aortic stiffness parameters changed with modified marsh classification. Most of the aortic elastic parameters had significant correlation with changes of tTG-IgA antibody in children with celiac disease. From the study also concluded that, most of the aortic elastic parameters had correlation with tTG-IgA antibody in celiac children. Suggested studies considering gluten free diet effect on aortic stiffness parameters in celiac children.

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7- CONFLICT OF INTEREST: None.

8- REFERENCES

1. Noori NM, Teimouri A. Evaluation of Gluten-free Diet on the Heart Functions in Children with Celiac Disease. International Journal of Pediatrics. 2019; 7(1):8889-905.

2. Noori NM, Teimouri A, Shahramian I, Shahraki T. Doppler Tissue Echocardiography and Electrocardiography in Children with Celiac Disease Compared to Controls. Int J Pediatr 2018; 6(11): 8561-78.

3. Heel DA, West J. "Recent advances in coeliac isease". Gut (Review), 2006; 55(7): 1037–46.

4. Lebwohl B, Ludvigsson JF, Green PH. Celiac disease and non-celiac gluten sensitivity. Bmj. 2015; 351: h4347.

5. Leeds JS, Hopper AD, Sanders DS. "Coeliac disease". Br Med Bull. 2008; 88 (1): 157–70.

6. Ciaccio EJ, Lewis SK, Biviano AB, Iyer V, Garan H, Green PH. Cardiovascular involvement in celiac disease. World journal of cardiology. 2017; 9(8):652.

7. Sethi S, Rivera O, Oliveros R, Chilton R. Aortic stiffness: pathophysiology, clinical implications, and approach to treatment. Integrated blood pressure control. 2014;7: 29.

8. Mozos I, Malainer C, Horbańczuk J, Gug C, Stoian D, Luca CT, Atanasov AG. Inflammatory markers for arterial stiffness in cardiovascular diseases. Frontiers in immunology. 2017;8:1058.

9. Cecelja M, Chowienczyk P. Arterial stiffening causes and consequences. Artery Res .2013; 7: 22–7.

10. Ljungberg J, Johansson B, Engström KG, Albertsson E, Holmer P, Norberg M, Bergdahl IA, Söderberg S. Traditional Cardiovascular Risk Factors and Their Relation to Future Surgery for Valvular Heart Disease or Ascending Aortic Disease: A Case–Referent Study. Journal of the American Heart Association. 2017; 6(5): e005133.

11. Bayar N, Çekin AH, Arslan Ş, Çağırcı G, Küçükseymen S, Çay S, Harmandar FA, Yeşil B. Assessment of Aortic Elasticity in Patients with Celiac Disease. Korean Circ J. 2016; 46: 239–45.

12. Bektaş O, Günaydin ZY, Bayramoğlu A, Kaya A, Karagöz A, Akgedik R. The effects of treatment in patients with childhood asthma on the elastic properties of the aorta. Cardiovascular journal of Africa. 2017; 28(3):165.'

13. Prenner SB, Chirinos JA. Arterial stiffness in diabetes mellitus. Atherosclerosis. 2015; 238(2):370-9.

14. Zapolski T, Furmaga J, Jaroszyński A, Wysocka A, Rudzki S, Wysokiński AP. The reverse remodeling of the aorta in patients after renal transplantation-the value of aortic stiffness index: prospective echocardiographic study. BMC nephrology. 2017; 18(1):33.

15. Korkmaz H, Sozen M, Kebapcilar L. Increased arterial stiffness and its relationship with inflammation, insulin, and insulin resistance in celiac disease. Eur J Gastroenterol Hepatol. 2015; 27:1193-1199.

16. Sari C, Ertem AG, Sari S, Efe TH, Keles T, Durmaz T, et al. Impaired aortic function in patients with coeliac disease. Kardiol Pol. 2015; 73:1108–13.

17. Noori N, Shahraki T, Teimouri A, Shahramian I. Cardiac Involvements in Patients with Celiac Disease by Doppler Tissue Echocardiography Compared to Conventional Echocardiography. International Cardiovascular Research Journal. 2018; 12(1):13-21.

18. Noori NM, Teimouri A, Keshavarz K, Moradi M. Assessment of Aortic Elasticity and the Doppler Tissue Echocardiography in Thalassemia Major Children. Journal of Child Science. 2020 Jan;10(01):e63-73.

19. Jansen H, Willenborg C, Schlesinger S, Ferrario PG, König IR, Erdmann J, Samani NJ, Lieb W, Schunkert H. Genetic variants associated with celiac disease and the risk for coronary artery disease. Mol Genet Genomics. 2015; 290:1911–17.

20. Demir AM, Kuloğlu Z, Yaman A, Fitöz S, Nergizoğlu G, Kansu A. Carotid intima-media thickness and arterial stiffness as early markers of atherosclerosis in pediatric celiac disease. Turk J Pediatr. 2016; 58:172-79.

21. Akin FE, Sari C, Özer-Sari S, DemirezerBolat A, Durmaz T, Keles T, et al. The evaluation of left ventricular functions with tissue doppler echocardiography in adults with celiac disease. Saudi journal of gastroenterology: official journal of the Saudi Gastroenterology Association, 2016; 22(2):116.

22. Noori NM, Teimouri A, Shahramian I, Shahraki T. Doppler Tissue Echocardiography and Electrocardiography in Children with Celiac Disease Compared to Controls. Int J Pediatr 2018; 6(11): 8561-78.

23. Fathy A, Abo-Haded HM, Al-Ahmadi N, El-Sonbaty MM. Cardiac functions assessment in children with celiac disease and its correlation with the degree of mucosal injury: Doppler tissue imaging study. Saudi J Gastroenterol. 2016; 22: 441-47.

24. Karpuz D, Tezol Ö, Kara B, Usta Y, Hallioğlu O. Determination of early atherosclerosis risk with aortic elasticity parameters in children with subclinical Celiac disease. Cukurova Med J 2018; 43(2):422-28.

25. Lewis NR, Scott BB. Systematic review: the use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests). Alimentary pharmacology & therapeutics. 2006; 24(1):47-54.

26. Dahlbom, I. R. Korponay-Szabo, J. B. Kov ´ acs, Z. Szalai, M. ´ Maki, and T. Hansson, Prediction of clinical and mucosal ¨ Severity of coeliac disease and dermatitis herpetiformis by quantification of IgA/IgG serum antibodies to tissue transglutaminase. Journal of Pediatric Gastroenterology and Nutrition. 2010 50(2):140–46.

27. Vivas S, de Morales JG, Riestra S, Arias L, Fuentes D, Alvarez N, et al. Duodenal biopsy may be avoided when high transglutaminase antibody titers are present. World journal of gastroenterology: WJG. 2009; 15(38): 4775.

28. Donaldson MR, Book LS, Leiferman KM, Zone JJ, Neuhausen SL. Strongly positive tissue transglutaminase antibodies are associated with Marsh 3 histopathology in adult and pediatric celiac disease. Journal of clinical gastroenterology. 2008; 42(3):256-60.

29. Hawamdeh H, Al-Zoubi B, Al Sharqi Y, Qasrawi A, Abdelaziz Y, Barbar M. Association of tissue transglutaminase antibody titer with duodenal histological changes in children with celiac disease. Gastroenterology research and practice. 2016; Article ID 6718590, 6 pages. http://dx.doi.org/10.1155/2016/6718590.

30. Rahmati A, Shakeri R, Sohrabi M, Alipour A, Boghratian A, Setareh M, Zamani F. Correlation of tissue transglutaminase antibody with duodenal histologic marsh grading. Middle East journal of digestive diseases. 2014; 6(3):131.

31. Paul B, Kinra P, Nandi B, Prasad AS. Correlation of Serum Tissue Transglutaminase Antibody Levels and Marsh Grading of Duodenal Biopsy in Patients of Celiac Disease. Annals of Pathology and Laboratory Medicine. 2019; 6(3): 142A-8A.

32. Güçlü A, Nar G, İçli A, Özhan N, Sezer S. Blood Pressure and Age Are the Main Determinants of Aortic Stiffness. Med Princ Pract 2017; 26:496. DOI: 10.1159/000480440

33. Jankowski P. Aortic Blood Pressure and Survival Study Group. Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. Hypertension. 2008; 51:848-55.

34. Ikonomidis I, Stamatelopoulos K, Lekakis J, Vamvakou GD, Kremastinos DT. Inflammatory and non-invasive vascular markers: the multimarker approach for risk stratification in coronary artery disease. Atherosclerosis. 2008 Jul 1;199(1):3-11.