Evaluation of Vascular Involvement in Children with Celiac Disease

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ABSTRACT

Aim: Celiac disease is associated with an increased risk of cardiovascular disease due to inflammation and autoimmunity involved in its pathophysiology. We aimed to evaluate vascular involvement in children with celiac disease based on their augmentation index, carotid pulse wave velocity, carotid intima-media thickness, echocardiographic findings, and blood pressure.

Materials and Methods: This cross-sectional and controlled study was performed at a single center between 2018 and 2019. The study population consisted of 44 patients with celiac disease who had been on a gluten-free diet for at least one year.

Results: We compared celiac patients with a healthy group. While the celiac patients had significantly higher carotid intima media thickness and carotid pulse wave velocity values, there was no difference in the augmentation index values. There was no significant difference in carotid artery intimal medial thickness, augmentation index and carotid pulse wave velocity values between the diet-compliant and non-compliant groups.

Conclusion: Although hypertension was not detected, arterial stiffness and carotid intima media thickness measurements were higher in the celiac disease patients compared to the healthy controls. This showed that these parameters can be used in early vascular damage assessment. These measurements, which are non-invasive and repeatable, can be a guide for the monitoring of the development of preclinical atherosclerosis in the follow-up of the pediatric patients diagnosed with celiac disease.

Keywords: AIx, celiac disease, children, cIMT, PWV

Introduction

Celiac disease (CD) is an immune-mediated condition characterized by inflammation triggered by dietary gluten and related prolamins and associated small intestinal villous atrophy (1,2). Genetic, immunologic and environmental factors are thought to be responsible for the development of CD (3,4).

CD is diagnosed using specific antibodies, such as tissue-transglutaminase antibody immunoglobulin-A antibody (tTG IgA), and screening followed by confirmatory small intestine biopsies (5). The only treatment is a life-long gluten-free diet (GFD). A GFD eliminates the gliadin and glutamine protein fractions contained in wheat, rye, and barley. Serological test values return to normal in 6-12 months after starting a strict GFD diet (6).

The risk of cardiovascular disease (CVD) in CD patients is still debated. Inflammation is associated with an increased risk of atherosclerosis (7,8). Atherosclerosis is

the most important risk factor for CVD and it begins in childhood. Patients at high risk of CVD can be identified by determining arterial thickness and elasticity (9-11). In the review study by Bernardi et al. (12), it was concluded that celiac patients should be screened for CVD risk. As subclinical atherosclerosis is reversible when detected and intervened early, the early diagnosis of arterial injury is important to prevent future vascular risk. Early diagnosis is possible by measuring increased carotid artery intimal medial thickness (cIMT), carotid pulse wave velocity (PWV) and the augmentation index (AIx). cIMT is evaluated by ultrasonography (13). Arterial stiffness can be assessed by the measurement of carotid PWV and AIx, which are the main indices for estimating arterial elasticity (14). These methods are repeatable, reliable, easy, and noninvasive techniques which can detect any increased arterial stiffness and thickness at an early stage (15).

CD is associated with an increased risk of CVD due to inflammation and autoimmunity (16-21). Additionally, the GFD contains high levels of fat, sugar and salt, and children with CD are exposed to excessive hypercaloric and hyperlipidemic products. Moreover, it is an unbalanced diet. A GFD may have a negative impact on cardiometabolic and cardiovascular risk factors, including obesity, increased serum lipid levels, insulin resistance, and cardiometabolic and cardiovascular risk factors leading to metabolic syndrome and atherosclerosis (22). In this study, we aimed to evaluate vascular involvement in children with CD based on their AIx, cIMT, carotid PWV, echocardiographic findings, and blood pressure.

Materials and Methods

This cross-sectional and controlled study was performed at a single center between 2018 and 2019. The study population consisted of 44 previously diagnosed biopsy-proven CD patients who had been on a GFD for at least one year.

There were no known co-morbidities such as hypertension (HT), dyslipidemia, systemic autoimmune disease, active infection, Mediterranean fever syndrome or selective immunoglobulin-A deficiency. The control group consisted of healthy children (n=35) of similar age and gender to the patient group who were admitted to the pediatric nephrology outpatient clinic. This study was approved by the Medical Research Ethics Committee of Ege University, Medical School (date: 17/12/2020, number: 20-12.1T/36). A written informed consent form was signed by the patients' parents or caregivers.

CD is diagnosed by a detailed clinical story, physical examination, laboratory tests and upper gastrointestinal endoscopy and biopsy.

The patients' age at the time of diagnosis, follow-up time, complaints, age, gender and family history were recorded. Their weight, height, body mass index (BMI) and standard deviation scores (SDS) at the initial and final visits were also recorded. All patients underwent weight measurement with a digital scale and height measurement with a stadiometer. SDS calculated according to Turkish growth charts were used to evaluate weight, height and BMI values in different age and gender groups (23).

IgA, tTG IgA, sedimentation rate and C-reactive protein were assessed after at least eight hours of fasting during the final visit. Samples were analyzed at a local laboratory. Tissue transglutaminase IgA antibody levels were measured by enzyme-linked immunosorbent assay.

Adherence to a GFD was assessed based on tTG IgA antibody levels. Tissue-transglutaminase IgA levels higher than 10 U/mL were considered positive and non-compliant to GFD.

Blood pressure was measured in the resting position using an Omron automatic blood pressure device and a suitable sized cuff. Average diastolic and systolic blood pressure values over 95% according to age, sex, and height after at least three measurements were considered as HT (24). Patients with HT underwent a 24-hour ambulatory blood pressure monitoring by the pediatric nephrology clinic. Echocardiogram (ECHO) was performed on those who had not had a cardiac evaluation within the previous six months.

The patients' carotid PWV, AIx and cIMT were measured. Carotid PWV and AIx were calculated using Vicorder three times (Skidmore Medical Limited, Bristol, UK). AIx was calculated as the difference between the first and second systolic peaks of the central aortic waveforms and defined as the percentage of the wavelength. For cIMT measurements, a Siemens Acuson Antares device and VFX-7-13-megahertz linear probe were used. Carotid intima-media thickness measurements were performed approximately 1 cm proximal from the bifurcation. All these measurements were performed by an experienced pediatric nephrologist.

Statistical Analysis

Statistical analysis was performed using basic statistical methods. The distribution of the data was calculated using the Kolmogorov-Smirnov normality test. The Independent

Samples t-test was used to compare numerical data between groups. Pearson's test was used to calculate the correlation between cIMT, carotid PWV and AIx with laboratory parameters. The significance level was accepted as p<0.05. The required sample size was calculated with the G-Power program to determine the difference in the evaluated parameters of both groups. The sample size was calculated to be a minimum of 8 people in each group and a total of 16 people. Data were analyzed using IBM SPSS 22.0 (IBM Corp., Armonk, NY) software package.

Results

Forty-four patients (28 females and 16 males) with CD having a mean age of 13.16±4.97 years were included in this study. Thirty-five age-matched (mean 14.00±4.01 years) subjects were selected as healthy controls. Of the healthy control group, 18 were female and 17 were male.

When the anthropometric measurements of the celiac group and the control group were compared, the values of the control group were found to be significantly higher than the celiac group (mean weight: 54.80±18.40 kg vs 42.34±15.19 kg, mean height: 156.74±16.52 cm vs 146.04±20.72 cm, respectively).

Thirty-six (81.8%) patients had classical (diarrhea, abdominal pain, and abdominal distention), five (11.4%) had atypical (short stature, anemia, and constipation) and three (6.8%) had silent types of CD, respectively.

Based on tTG IgA antibody results, 22 (50%) patients were considered to be compliant with the GFD. The anthropometric measurements of the CD patients are presented in Table I.

The mean of three blood pressure measurements indicated stage 2 HT in only one of the CD patients who was 19 years old. Stage 1 HT was detected as a result of twenty-four hours of ambulatory blood pressure monitoring. There were no pathological findings of HT in his ECHO evaluation. The other patients had normal blood pressure and ECHO results.

There was no significant difference between the anthropometric measurements, biochemical parameters, cIMT, AIx and carotid PWV values in the diet-compliant and non-compliant groups (Table II).

We compared the celiac patients and the healthy group. While the celiac patients had significantly higher cIMT and carotid PWV values, there was no difference in the AIx values (Table III).

The celiac patients had no significant relationship between their tTG IgA antibody and carotid PWV, cIMT and AIx levels. However, there was a significant negative relationship between their AIx and height (r=-0.575, p<0.001), weight (r=-0.609, p<0.001) and BMI (r=-0.459, p=0.002) and positive relationships between their carotid PWV and weight (r=0.362, p=0.016) and BMI (r=0.387, p=0.01) in those children with CD. There was a significant positive relationship between their cIMT and height SD values (r=0.558, p=0.001).

Table I. Anthropometric measurements of the CD patients (n=44) at the time of diagnosis

	Minimum	Maximum	Mean ± SD
Height (cm)	81.0	160.0	126.32±25.28
Height SD	-4.12	2.74	-1.14±1.55
Weight (kg)	11.0	61.0	29.15±14.13
Weight SD	-3.30	1.50	-1.11±1.32
BMI (kg/m²)	13.22	22.32	16.89±2.48
BMI SD	-2.80	1.44	-0.53±1.09

CD: Celiac disease, SD: Standard deviation

Table II. Comparative analysis of the demographic, anthropometric and biochemical data of tTG IgA antibody positive and negative CD patients

	Patients with tTG IgA antibody (+) Mean ± SD (n=22)	Patients with tTG IgA antibody (-) Mean ± SD (n=22)	p-value
Age (year)	13.50±5.61	13.50±4.38	0.99
Weight (kg)	41.21±16.34	43.47±14.25	0.62
Weight SD	-0.47±1.27	-0.53±1.42	0.90
Height (cm)	145.00±23.31	147.09±18.25	0.74
Height SD	-0.78±1.38	-0.55±1.53	0.66
BMI (kg/m²)	18.52±3.14	19.42±3.77	0.40
BMI SD	-0.14±1.17	-0.36±1.34	0.64

CD: Celiac disease, SD: Standard deviation, tTG IgA: Tissue-transglutaminase antibody immunoglobulin-A antibody

Table III. Comparative analysis of the cIMT, AIx, and carotid PWV values of the CD patients and the healthy control group on the final visit

	CD patients Mean ± SD (n=44)	Mean ± SD (n=35)	p-value
cIMT	0.51±0.05	0.45±0.08	0.001
Carotid PWV	4.82±0.42	4.59±0.29	0.001
AIx	25.93±15.27	22.54±7.96	0.238

CD: Celiac disease, SD: Standard deviation, cIMT: Carotid artery intimal medial thickness, AIx: Augmentation index, PWV: Pulse wave velocity

Discussion

There is limited data on vascular involvement in pediatric CD patients. Our study is the first report evaluating preclinical atherosclerosis in pediatric celiac patients using carotid PWV, AIx, cIMT measurements; ECHO and blood pressure values.

Inflammation plays an important role in the pathogenesis of atherosclerosis. Chronic inflammation may be responsible for the development of atherosclerosis in pediatric CD. However, the autoimmune nature of CD has also targeted other organ systems, including the cardiovascular system. Some studies in adult CD patients have suggested that CD is associated with early atherosclerosis (25,26). In a multicenter study conducted in 2013, 14% (n=114) of CD patients were shown to have at least one traditional CVD risk factor and screening for CVD risk factors in CD was recommended both at the time of diagnosis and during follow-up (8). A significant increase in PWV and cIMT was observed in adults with CD compared to the control group (25-27). All these findings suggest that preclinical atherosclerosis may be common in adults with CD. Atherosclerosis is known to start in childhood; however, symptoms usually appear at older ages. Studies have demonstrated that an earlier onset increases the chance of atheromatous plaque formation. Therefore, the early detection and intervention of the development of atherosclerosis in childhood are crucial in terms of decreasing the mortality and morbidity which can be observed in older ages. In a pediatric population study, cIMT and PWV values were not different in CD patients compared with healthy controls (28). In the present study, we found that cIMT and carotid PWV values were significantly higher in the CD patients (mean 0.51±0.05 vs. 0.45±0.08, mean 4.82±0.42 vs. 4.59±0.29, respectively). In our study, another important finding was the insignificant increase in AIx in CD patients compared to the healthy controls. Multicenter and larger sample size studies may be needed to obtain a statistically significant difference regarding this.

There is a correlation between the presence of CD-specific antibodies and disease severity. In contrast to three other studies, no significant difference was found between tTG IgA antibody positive and negative subjects in terms of carotid PWV, AIx and cIMT in this study. It might be considered that the normal ranges of serologic tests should be reviewed (25,28,29).

There was a positive relationship between the cIMT and tTG IgA antibody levels in a study conducted in pediatric age group CD patients (28). However, in our study, CD patients had no significant relationship between tTG IgA antibody and carotid PWV, cIMT, or AIx levels. Therefore, arterial thickness and elasticity may be affected by uncontrolled or undiagnosed CD as well as other unknown factors. There was a significant negative relationship between AIx and height (r=-0.575, p<0.001), weight (r=-0.609, p<0.001) and BMI (r=-0.459, p=0.002). There was a significant positive relationship between cIMT and height SD values (r=0.558, p=0.001). There was a significant positive relationship between carotid PWV with weight and BMI values (r=0.362, p=0.016, r=0.387, p=0.010, respectively) as was previously shown in the pediatric CD patients (28).

The blood pressure values of the CD patients, except for one, were within the normal range. A 19-year-old male patient with stage 1 HT had diet compliance problems. We learned that this patient had been smoking a packet of cigarettes per day for the last three years. Uncontrolled CD and smoking were the probable cause of HT in this subject. The development of HT may be related to tTG IgA antibody positivity and result in inflammatory activity by causing atherosclerosis.

Study Limitations

Our study had a few limitations such as the small number in the patient group, the lack of cIMT, AIx and carotid PWV measurements before starting a GFD and the lack of CVD risk factors data for both the CD patients and the healthy controls.

Conclusion

In conclusion, although HT was not detected, arterial stiffness and cIMT measurements were higher in the CD

patients compared to the healthy controls. This shows that such parameters can be used in early vascular damage assessment. These measurements, which are non-invasive and repeatable, can be a guide for monitoring the development of preclinical atherosclerosis in the follow-up of CD patients.

Ethics

Ethics Committee Approval: This study was approved by the Medical Research Ethics Committee of Ege University, Medical School (date: 17/12/2020, number: 20-12.1T/36).

Informed Consent: A written informed consent form was signed by the patients' parents or caregivers.

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Authorship Contributions

Surgical and Medical Practices: E.K.T., E.D., C.K., E.L., Concept: E.K.T., S.T., İ.K.B., E.L., F.Ç., S.A., Design: E.K.T., E.D., M.K., İ.K.B., C.K., E.L., S.A., Data Collections or Processing: E.K.T., S.T., M.K., İ.K.B., C.K., E.L., Analysis or Interpretation: E.K.T., S.T., E.D., M.K., F.Ç., S.A., Literature Search: E.K.T., E.D., M.K., F.Ç., Writing: E.K.T., İ.K.B., F.Ç., S.A.

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