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Abstract

Objective: The possible relationship of attention-deficit/hyperactivity disorder (ADHD) with cardiovascular disease risk by subclinical atherosclerosis in children rarely investigated in the literature. The aim of this case-controlled study is to evaluate chronic inflammation, subclinical atherosclerosis and cardiovascular disease risk in children and adolescents with ADHD.

Methods: A total of 51 medication-free children and adolescents with ADHD and 51 healthy controls were included in this study. The Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version was used to determine the diagnosis of ADHD and other psychiatric disorders. Conners' Parent Rating Scale-Revised Short Form and the Conners' Teacher Rating Scale-Revised Short Form severity of ADHD was used to evaluate severity of ADHD. In order to evaluate subclinical atherosclerosis, common carotid intima media thickness (IMT), epicardial adipose tissue thickness (EAT), and periaortic adipose tissue thickness (PAT) were assessed as well as clinical parameters.

Results: The IMT (0.037 cm ±0.005 cm vs. 0.026 cm ± 0.003 cm), EAT (0.472 cm ± 0.076 cm vs. 0.355 cm ± 0.051cm), and PAT (0.135 cm ± 0.016 cm vs. 0.118 cm ± 0.009 cm) measurements were significantly higher in the ADHD group than in the control group. Additionally, partial correlation analyses revealed that a positive correlation was observed between IMT and EAT, and PAT measurements separately. Multivariate linear regression analysis revealed that, body mass index (BMI) positively predicted IMT. Also, age and BMI positively predicted the EAT levels of the subjects with ADHD.

Conclusions: Subclinical atherosclerosis is an important early marker for cardiovascular diseases especially at advancing age. Also, chronic inflammation may be the underlying mechanism. Our results suggest that children and adolescents with ADHD have a risk for cardiovascular disease. For this reason, subclinical atherosclerosis should be taken into consideration in the follow-up and treatment of ADHD for cardiovascular disease risk.

Keywords: attention-deficit/hyperactivity disorder; intima-media thickness; epicardial adipose tissue thickness; periaortic adipose tissue thickness; chronic inflammation; cardiovascular disease

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with an onset during childhood, characterized by inattention, hyperactivity and executive dysfunction (1). ADHD has a worldwide prevalence of 5.9 – 7.1% for children and adolescents (2). The pathophysiology of ADHD is complex and includes biochemical, psychological, genetic, and environmental factors (3). Although a common disorder, the pathophysiologic mechanisms of ADHD are not completely understood. In recent years, increasing evidence indicates a critical role for chronic inflammation as a pathophysiologic mechanism for ADHD (4).

Atherosclerosis (AS) is a condition characterized by a long, initial, asymptomatic phase and atherosclerotic heart disease is one of the leading causes of mortality all over the world. Although adverse clinical outcomes usually occur in middle age, atherosclerotic heart disease is known to develop early in life (5). The progression of subclinical and asymptomatic atherosclerotic heart disease over the years can lead to a variety of acute coronary events such as acute myocardial infarction, unstable angina or sudden cardiac death (6). By this way, subclinical AS is a precursor of cardiovascular diseases (CVD) which is highly prevalent in people with optimal control of the risk factors, and has been shown most often using intima-media thickness or the presence of carotid plaque as diagnostic criteria (7). Various invasive and noninvasive imaging modalities have allowed detection of early and subclinical atherosclerotic lesions, as well as examination of the natural history of these lesions as it relates to plaque progression and plaque instability (6). Because plaque progression is a necessary and modifiable step between subclinical AS and an acute coronary event, early detection of subclinical AS leads to early treatment. Also, there are non-modifiable risk factors for the AS, as well as the modifiable/lifestyle risk factors, such as hypertension, dyslipidemia, smoking, obesity, and metabolic diseases (8). In this context, subclinical AS has been the subject of several studies because it develops early in life and is an important marker of the possible risk of CVD. However, studies of children and adolescents on this issue are limited in number and have complex results. One of the most commonly used markers in research for this purpose is common carotid intima media thickness (IMT) which an important marker for early AS that can be measured easily in a non-invasive manner. There

are various studies suggesting that high IMT levels in mood disorders such as depression and bipolar disorder in youth are associated with CVD risk (9). There is only one study in which CVD risk was determined by evaluating IMT levels in children and adolescents with ADHD (10). However, epicardial adipose tissue (EAT) thickness, and periaortic adipose tissue (PAT) were not evaluated in the study. By this way, as a significant indicator of subclinical AS, IMT, EAT and PAT are associated with subsequent risk of CVD (11–13).

On the other hand, atherosclerosis is a chronic disease in which inflammation plays an important role at all stages, from development and progression to the determination of incident clinical events (14). The relationship between ADHD and inflammation has been investigated in several studies from various aspects. Evidence for this relationship comes mainly from: (1-) studies showing a strong association between ADHD and autoimmune and inflammatory disease; (2-) studies reporting increased serum levels of inflammatory markers in ADHD; and (3-) evidence from genetic studies (15). Additionally, a recent study suggested that anti-cytokine therapy could be a promising aspect in moderating atherogenesis, especially when initiated in the early stages of subclinical AS (16). So, all these studies suggest that chronic inflammation is the main underlying disease of subclinical AS.

To our knowledge, there is only one study about the relationship of ADHD and subclinical AS by measuring IMT as a risk factor of CVD. Also, there is no study about the relationship of ADHD and subclinical AS by measuring EAT and PAT. The aim of this study was to evaluate IMT, EAT, and PAT as indicators of subclinical AS in children and adolescents with ADHD as compared with healthy controls.

Materials and Methods

Participants

The study sample group was recruited from the outpatient clinic of the child and adolescent psychiatry department of a children's hospital. The group comprised treatment-naive children and adolescents aged 8–17 years who were diagnosed as having ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. The exclusion criteria were the presence

of major physical, cardiological, endocrinological (such as familial hypertriglyceridemia or hypercholesterolemia), or neurologic diseases, obesity, comorbid psychiatric disorders, and smoking. Participants who had previously used psychotropic drugs prior to admission were also excluded from the study to prevent the bias in the study population. The average duration of the disorder was calculated by considering the time between the onset of ADHD symptoms and diagnosis. The control group consisted of healthy volunteer children and adolescents aged 8-17 years. The same exclusion criteria were applied to the healthy control group. Subjects who had any psychiatric disorders in the healthy control group were also excluded from the study. A semi-structured interview (The Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version (K-SADS-PL)) was applied to all participants.

All the children were examined by the same physician at the time of their recruitment into the study. Their height and weight were obtained by standard measurements. We calculated the body mass index (BMI) using the formula BMI=weight (kg)/height(m)^2 and the patients with the values ≤24.9 kg/m^2 with age- and sex-adjustment, based on the national reference data were included in the study (17).

Blood pressure (BP) was measured with an appropriately sized cuff with a standardized automated Dinamap on the right arm in the sitting position after a 3-min rest period. Also, a 12-lead surface electrocardiogram was performed for all subjects.

The study was approved by the ethics committee of Karatay University with the number 2020/002 and all procedures were conducted in accordance with the Declaration of Helsinki and local laws and regulations. The participants and their parents gave their written informed consent after the investigators explained the aim and course of the study. Oral assent was also obtained from all participants.

Procedures

K-SADS-PL was administered to the patients and control subjects by experienced child and adolescent psychiatrists for diagnosis and to determine comorbid psychiatric disorders (18,19). The diagnoses of ADHD were made based on the DSM-5 criteria. Parents and school teachers of the participants

completed the Conners' Parent Rating Scale-Revised Short Form (CPRS) and the Conners' Teacher Rating Scale-Revised Short Form (CTRS) (20,21). The reliability and the validity of all scales were previously established for our native language (22,23). After completion of psychiatric assessments, height, weight, blood pressure, BMI and echocardiography measurements of the children were made by the same pediatric cardiologist.

Psychological Measures/Instrumentation

The Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version (K-SADS-PL)

K-SADS-PL is a semi-structured interview method used to identify psychiatric disorders in children and adolescents. It can detect both present and past psychiatric disorders. It is applied face-to-face to children, adolescents and their parents. The conclusion is reached by taking into account the information received from the teacher, parents, and the child or adolescent. If conflicting data are obtained from different sources, the clinician uses his/her clinical judgment to settle the issue. A validity and reliability study was conducted for our nation (18,19).

The Conners' Parent Rating Scale-Revised Short Form (CPRS) and The Conners' Teacher Rating Scale-Revised Short Form (CTRS)

CPRS and CTRS are questionnaires used in the diagnosis and follow-up processes of ADHD and administered to parents and teachers respectively. They are a 4-point Likert type. The score value for each item varies between 0-3. A high score indicates that the child has more of the problems described in the questionnaire about ADHD. Validity and reliability studies of both questionnaires were conducted for our nation (20–23).

Echocardiographic Measurements

M-Mode Echocardiographic Measurements

Echocardiographic investigations were performed using a Philips Affiniti 50 device (Philips Healthcare, Andover, The Netherlands) with 2.0-4.0 MHz transducers. All measurements were

performed according to the American Society of Echocardiography by the same observer who was blinded to the patients' clinical details (24). The measurements were obtained during three consecutive cardiac cycles and the average values were computed. Ejection fraction (EF) and fractional shortening (FS) of the left ventricle (LV), right ventricle (RV), interventricular septum systolic (IVSs) and diastolic (IVSd) thickness, LV end-systolic and end-diastolic dimensions, and LV posterior wall systolic (LVPWs) and diastolic (LVPWd) thicknesses were measured from M-mode echocardiographic tracings obtained at the midchordal level in the parasternal long axis view. The left ventricular mass (LVM) was estimated by using the anatomically validated formula of Devereux and Reichek (25). The left ventricular mass index (LVMI) was calculated by dividing the LVM to the height as previously described by de Simone et al. (26).

Measurement of Common Carotid Artery Intima-Media Thickness

Longitudinal images of the common carotid artery were obtained using the 2-dimensional (2D) mode and color Doppler examinations combined. Patients' heads were turned 45° toward the side opposite the side being examined. Also, patients' carotid arteries were angled as perpendicular to the plane of sound as possible. The depth of echocardiographic device increased to 90 Hz for all measurements. The lateral (90°), anterior (45°) and posterior (135°) projections in the distal wall followed an axis perpendicular to the artery to distinguish between two lines: one for the intima–blood interface and the other for the media–adventitious interface. The common carotid artery IMT measurement protocol consisted of scanning each of the carotid arteries in three segments: (1) the near wall and far wall of the segment extending from 10 to 20 mm proximal to the tip of the flow divider into the common carotid artery; (2) the near wall and far wall of the carotid bifurcation beginning at the tip of the flow divider and extending 10 mm proximal to the flow divider tip; and (3) the near wall and far wall of the proximal 10 mm of the internal carotid artery. On a longitudinal echocardiographic image, the posterior wall of the carotid artery was displayed as two bright white lines separated by a hypoechogenic space (27). The mean IMT was calculated from three consecutive measurements.

Measurement of Epicardial Adipose Tissue Thickness

The epicardial adipose tissue was identified as an echo-free space in the pericardial layers on 2D echocardiography, and its thickness was measured perpendicularly on the free wall of the RV at end-diastole from the parasternal long-axis views (28). Also, the depth of echocardiographic device increased to 90 Hz for all measurements. The mean EAT was calculated from three consecutive measurements.

Measurements of Periaortic Adipose Tissue Thickness

Measurement of perivascular adipose tissue wew performed using conventional methods from the adventitia layer of the abdominal aorta and the adventitial layer of the aorta adjacent to the form of the measurement of the linear echogenic line. Periaortic adipose tissue cannot be directly distinguished with echocardiographic and ultrasonographic images in deep tissue. Therefore, it should be measured with adventitia. Measurements were taken in the axial plane in the supine position at the L1–2 level (just above the umbilicus), proximal to the iliac bifurcation (12,29). Also, patients' abdominal aortas were angled as perpendicular to the plane of sound as possible and the depth of echocardiographic device increased to 90 Hz for all measurements. Evaluations were repeated three times and the mean value was calculated.

Statistical Analysis

The normality of distribution of continuous variables was tested by Shaphiro Wilk test. First, Student t (for normal data) and Mann Whitney u test (for non-normal data) and Chi-square test (categorical data) were used to compare 2 independent groups. Partial correlation coefficients were calculated to investigate relationship between numerical variables. Multivariate linear models were built for adjusting effect of possible confounding factors and estimating adjusted beta coefficients. While building models, multicollinearity was checked by calculating variance inflation factors (VIF). Variables were included to model when VIF is smaller than 2. Intraobserver variability was assessed using Pearson’s correlation analysis, coefficient of variance, and Bland-Altman analysis. All statistical analysis was performed with SPSS for Windows version 24.0 and a P value < 0.05 was accepted as statistically significant.

Results

The study consisted of 51 children and adolescents with ADHD and 51 healthy controls. The mean age of the children and adolescents with ADHD was 11.02 ± 2.1 (range, 8–17) years; the ADHD study sample consisted of 38 (74.5 %) boys and 13 (25.5 %) girls. The mean age of the healthy control group was 11.2 ± 2.1 years (range = 8–17 years); the healthy control group consisted of 32 (62.7 %) boys and 19 (37.3 %) girls. There is no statistically significant difference between the groups in terms of age and gender distribution (p=0.524, p=0.200 respectively). The average duration of the disorder in patients with ADHD was 3.92±2.39 years. The study groups were similar in terms of family income and parents' educational levels. Table 1 presents and compares the descriptive data, socioeconomic variables and patients the clinical variables of the study groups. No significant differences were found between the groups in terms of BMI, systolic blood pressure (BP-S), diastolic blood pressure (BP-D), mean blood pressure, and other descriptive data and, socioeconomic variables. On the other hand, in the comparison of psychometric measurements CPRS-RS and CTRS-RS scores were significantly higher in the ADHD group than in the healthy control group ($p<0.001$ for both).

Table 2 presents and compares the M-mode echocardiographic measurements of the study groups. Statistically, no significant between-group differences were found for EF, FS, IVSd, LVPWs, LVPWd, LVM, LVIDs, LVIDd, IVSs, and LVMI measurements ($p>0.05$ for all). Additionally, the significance levels did not change when the parameters were analyzed according to gender, age, BMI, mean blood pressure and socioeconomic status levels (P adjusted >0.05 for all) (Table 2).

On the other hand, the comparison of IMT, EAT, and PAT measurements of the groups revealed a significant statistically difference between the two groups. The IMT (0.037 cm ± 0.005 cm vs. 0.026 cm ± 0.003 cm), EAT (0.472 cm ± 0.076 cm vs. 0.355 cm ± 0.051 cm), and PAT (0.135 cm ± 0.016 cm vs. 0.118 cm ± 0.009 cm) measurements were found to be higher in the ADHD group than in the healthy control group ($p<0.001$ for all) Also, the significance levels did not change when the parameters were analyzed according to gender, age, BMI, mean blood pressure and socioeconomic level values (Padjusted<0.001 for all) (Table 3).

According to the partial correlation analyses, a positive moderate correlation was observed between IMT and EAT, and PAT measurements separately ($p<0.001$ for both) (Table 4)**.** Also, a positive correlation was observed between CPRS-RS and CTRS-RS ($p<0.05$ for both). However, no significant correlation was found between the IMT, EAT, PAT measurements and CPRS-RS, CTRS-RS and duration of ADHD ($p>0.05$, for all).

The psychological variables predicting the IMT, EAT, and PAT levels were determined using multivariate linear regression in the patients with ADHD. As shown in Table 5, BMI positively predicted the IMT levels in the regression analysis model ($p=0.040$). Age and BMI positively predicted the EAT levels of the subjects with ADHD ($p=0.004$, $p=0.001$).

Intraobserver variability of EAT and common carotid artery IMT measurements were less than 6.1% (0.2%-9.3%). Also, intraobserver variability of ultrasonographic evaluation was low (coefficient of variation=5%-9%).

Discussion

The aim of this study was to assess the early development of subclinical AS in children and adolescents with ADHD. In this study, IMT, EAT, and PAT values were significantly higher in children and adolescents with ADHD than in healthy controls. This result reveals the presence of subclinical AS and the risk of CVD in children and adolescents with ADHD.

The relationship between ADHD and chronic inflammation has been investigated in many studies. Akıncı and Uzun, who demonstrated the relationship between ADHD and chronic inflammation in relation with systemic inflammatory response, reported that neutrophil lymphocyte ratio, platelet lymphocyte ratio and white blood cells were higher in children with ADHD as compared with healthy children (30). Additionally, a case-controlled study demonstrated that serum levels of interleukin (IL)-6 were significantly higher in patients with ADHD than in healthy controls (31). Chronic exposure to inflammation may be a risk factor for CVD by adversely affecting endothelial functions through proinflammatory cytokine, causing subclinical AS. (32,33). In addition, in a meta-analysis, chronic inflammation was found independently associated with higher IMT levels (34). So, our data with the

related literature suggest that chronic inflammation may be an underlying mechanism for subclinical AS in children and adolescents with ADHD.

AS heart disease is one of the leading causes of mortality all over the world. In this context, subclinical AS has been the subject of several studies because it develops early in life and is an important marker of the possible risk of a CVD (5,6). However, studies of children and adolescents on this issue are limited in number and have complex results. One of the most commonly used markers in research for this purpose is IMT which an important marker for early AS that can be measured easily in a non-invasive manner. IMT is a reliable indicator of children's cardiovascular health and is a reliable marker in assessing subclinical AS (35). On the other hand, IMT measurements were investigated in many studies where chronic inflammation-related subclinical AS in childhood was evaluated (32,36). It has been shown in various longitudinal studies that neglect, abuse, familial stresses, and chronic life stresses in childhood are associated with high IMT levels and this causes subclinical CVD (37–39) . Studies conducted in various age groups have found that ADHD causes psychological and cellular stress (40–42). In psychiatric diseases known to cause chronic inflammation, IMT measurements in terms of CVD risk were studied in a limited number of studies. In a long follow-up study by Keltikangas-Järvinen et al. that investigated cardiovascular risks through psychiatric symptoms in children, hyperactivity behavior in childhood was found to be associated with higher IMT levels in adulthood (43). However, in this study, hyperactivity was evaluated as a symptom and ADHD diagnosis was not taken into consideration. In the study conducted by Öğütlü et al. in children and adolescents with ADHD, it was shown that IMT values were higher in ADHD patients compared to the control group (10). American Heart Association have stated that mood disorders like depression and bipolar disorder pose a risk for CVD by causing AS in youth (9). It has also been shown that depressive symptoms are associated with high IMT levels in young adult males but not females (44). In addition, IMT values were found to be high in studies conducted in adults with symptoms of depression and anxiety (45,46). On the other hand, in a study conducted with depressed adolescents, it was shown that there was no relationship between IMT levels and depression (47). Similarly, in a study examining the relationship between chronic life stresses and cardiovascular

disease in adolescents, no relationship was found between chronic stress, cardiovascular reactivity and IMT (39). However, in a study with different results, it was found that depression in middle-aged and older adults was associated with high IMT levels, independent of cardiovascular comorbidities (48). These data suggest that the relationship between mood disorders observed in later ages and IMT may be related to age. There is a significant inconsistency in the results of studies in the literature on the risk that mood disorders cause for CVD by causing AS. For this reason, we included pure ADHD cases in our study in order to show that stress and inflammation, which we think that only ADHD causes, increase CVD risk by excluding various comorbid disorders in ADHD. In our study, IMT levels were found to be elevated in children and adolescents with ADHD compared with healthy controls ($p<0.001$). Our results are similar to the research of Öğütlü et al. (10), which is the only one in the literature on this subject. This result reveals that ADHD is a chronic inflammatory process and leads to the development of subclinical AS in children and adolescents, causing significant risk for CVD later in their lives. On the other hand, the recommendations of American Heart Association for noninvasive assessment of subclinical atherosclerosis in children and adolescents revealed different normal values of IMT for each age groups (49). However, in our study we could not evaluate the study population for each age groups because of the limited number of cases.

Epicardial adipose tissue is a visceral fat deposit that surrounds the heart. The increase in epicardial adipose tissue causes direct or indirect adverse effects in coronary arteries and myocardial tissue (50). Hirata et al. reported that inflammatory cell infiltration increased in epicardial adipose tissue, but this increase was not present in subcutaneous adipose tissue, indicating that epicardial adipose tissue might cause chronic inflammation, leading to coronary AS (51). The increase in EAT is associated with subclinical AS and CVD in individuals (52). Therefore, EAT measurements are an important parameter that can be monitored in assessing CVD risk and as a treatment target (52). In this study, EAT values were found to be significantly higher in children and adolescents with ADHD than in healthy controls ($p<0.001$).

Periaortic adipose tissue is visceral fat deposits that surround the aorta, causing inflammation and AS, affecting vascular functions (53). Increased PAT is known to pose a significant risk for CVD (13)..

The relationship between PAT and AS and CVD in children has been investigated in a number of studies. PAT has been shown to be significantly elevated in childhood disorders, such as type 1 DM compared with healthy children, and has been suggested as an important risk factor for CVD (54). However, there was no study in the literature that investigated the relationship between psychiatric diseases and PAT. In the present study, PAT values were found to be significantly higher in children with ADHD than in the healthy control group ($p<0.001$). There is no study evaluating CVD risk by measuring EAT and PAT in patients with ADHD.

It has been shown that IMT was correlated with both EAT and PAT in studies that investigated subclinical AS and CVD risk by measurements of IMT, EAT, and PAT (53,55). Sengül et al. found that IMT and EAT levels were positively correlated in patients with metabolic syndrome (55). Yun et al. revealed that elevated PAT had an independent relationship with elevated IMT (56). Similarly, IMT levels were found to be correlated with both EAT and PAT levels in this study (56). Also, our data suggest that IMT, EAT, and PAT are important markers in assessing the risk of CVD in children and adolescents with ADHD. On the other hand, BMI is known to be an important predictor for IMT and EAT (57). Additionally, it is suggested that EAT measurements will provide more accurate results in assessing CVD risks in patients with normal BMI (58). In our study it was showed that BMI positively predicted IMT and EAT levels. Also, while age and BMI levels were found to predict EAT levels.

This study has some limitations. The most important limitation is the limited number of cases. However, the data reliability increased because of the number of cases, which was limited due to reasons such as the sole inclusion of patients with ADHD, conducting semi-structured interviews with each patient, collecting data from different sources such as parents and teachers, and considering these patients for cardiologic evaluation. Secondly, due to the limited number of cases, we could not evaluate whether there were differences between the subtypes of ADHD within the context of the parameters investigated. Lastly, thyroid-stimulating hormone (TSH) and any chemical biomarkers that show chronic inflammation and lipid profiles were not analyzed in the study.

Conclusions

In conclusion, we found that IMT, EAT and PAT were higher in children and adolescents with ADHD, and therefore they were at risk for CVD. Chronic inflammation may be an underlying mechanism for subclinical AS in these patients. Accordingly, subclinical AS and associated complications should be considered in the treatment and follow-up of patients with ADHD. Future studies are needed to determine the effects of subclinical AS in adulthood for detecting CVD risk in ADHD patients and to evaluate the role of drugs used in ADHD treatment in the development of subclinical AS.

Conflicts of interest

None

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Table 1. Demographic and clinical characteristics of the participants.

Variables	ADHD Group (n:51)	Control Group (n:51)	p Value
Age (years)	11.02±2.18	11.29±2.15	0.524
Boy/Girl (n/%)	38(74.5)/13(24.5)	32(62.7)/19(37.3)	0.200
Body Mass Index (kg/m^2)	18.88±2.74	18.17±2.28	0.158
Systolic Blood Pressure (mmHg)	103.82±12.63	102.75±9.6	0.903
Diastolic Blood Pressure (mmHg)	68.43±8.33	66.08±7.5	0.140
Mean Blood Pressure (mmHg)	80.22±8.83	78.3±7.67	0.242
CPRS-RS	48.51±11.66	22.63±8.48	**<0.001**
CTRS-RS	45.45±11.59	23.27±9.55	**<0.001**

*Significant at 0.05 level; Chi-square test for categorical data, Mann Whitney U and Student t test for numerical data.

CPRS-RS: Conners' Parent Rating Scale-Revised Short

CTRS-RS: Conners' Teacher Rating Scale-Revised Short

Table 2. Comparison analyses for M-mode echocardiographic measurements among the groups

Variables	ADHD Group	Control Group	p Value	$P_{adjusted}$
LVPWs (mm)	1.24±0.15	1.2±0.16	0.385	0.492
LVIDs (mm)	2.44±0.29	2.42±0.3	0.976	0.900
IVSs (mm)	1.24±0.18	1.24±0.14	0.908	0.874
LVPWd (mm)	0.72±0.1	0.71±0.19	0.879	0.964
LVIDd (mm)	4.15±0.43	4.08±0.34	0.296	0.511
IVSd (mm)	0.68±0.1	0.67±0.12	0.339	0.397
EF (%)	72.06±5.45	72.63±8.73	0.969	0.825
FS (%)	41.07±4.7	40.35±4.98	0.217	0.292
LVM (mm)	89.07±24.31	81.66 ±26.82	0.316	0.571
LVMI (mm)	31.77±7.2	29.21±6.25	0.112	0.234

$P_{adjusted}$: Multivariate linear model results adjusted by gender, age, BMI, mean blood pressure and socioeconomic level.
LV: Left ventricle, EF: Ejection fraction
FS: Fractional shortening, IVSs: Interventricular septum systolic thickness
IVSd: Interventricular septum diastolic thickness, LVPWs: LV posterior wall systolic thicknesses
LVPWd: LV posterior wall diastolic thicknesses, LVM: Left ventricular mass
LVMI: Left ventricular mass index, LVIDs: LV end-systolic dimensions,
LVIDd: LV end-diastolic dimensions

Table 3. Comparison analyses for IMT, EAT, PAT measurements between the groups

Variables	ADHD Group	Control Group	p Value	$P_{adjusted}$
IMT (cm)	0.037±0.005	0.026±0.003	<0.001	<0.001
EAT (cm)	0.472±0.076	0.355±0.051	<0.001	<0.001
PAT (cm)	0.135±0.016	0.118±0.009	<0.001	<0.001

Padjusted: Multivariate linear model results adjusted by gender, age, BMI, mean blood pressure and socioeconomic level.
SD: Standart Deviation, IMT: Common Carotid Artery Intima-Media Thickness
EAT: Epicardial Adipose Tissue Thickness, PAT: Periaortic Adipose Tissue Thickness

Table 4. Partial correlations of the IMT, EAT and PAT measurements with psychological variables

Variables	IMT	EAT	PAT	Duration	CTRS-RS	CPRS-RS
IMT	1					
EAT	**.192****	1				
PAT	**.459****	-.116	1			
Duration	-.059	-.226	.120	1		
CTRS-RS	-.053	-.063	.087	-.126	1	
CPRS-RS	.005	.065	.086	-.104	**.336***	1

*p<0.05, **p<0.001, Partial correlation coefficients controlled by gender, age, BMI and socioeconomic level. IMT: Common Carotid İntima Media Thickness, EAT: Epicardial Adipose Tissue Thickness, PAT: Periaortic Adipose Tissue Thickness, Duration: Duration of ADHD, CTRS-RS: Conners' Teacher Rating Scale-Revised Short, CPRS-RS: Conners' Parent Rating Scale-Revised Short, Duration: Duration of ADHD (years).

Table 5. The associated parameters with IMT, EAT, PAT measurements according to multivariate linear regression analysis

Variables*	IMT		EAT		PAT	
	β	p	β	p	β	p
Age	.001	.650	**.013**	**.004***	.002	.171
Gender	-.003	.144	-.020	.303	.002	.762
Body Mass Index	**.001**	**.040***	**.013**	**.001***	.001	.328
Mean Blood Pressure	.001	.355	.001	.593	.001	.917
Socioeconomic level	-.001	.421	-.007	.502	.004	.208

*Significant at 0.05 level

*Dependent Variables: IMT: Common Carotid Artery Intima-Media Thickness

EAT: Epicardial Adipose Tissue Thickness, PAT: Periaortic Adipose Tissue Thickness