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RESEARCH

Evaluation of arterial stiffness in patients with generalized anxiety disorder

Yaygın anksiyete bozukluğu olan hastalarda arteriyel sertliğin değerlendirilmesi

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Abstract

Purpose: Generalized anxiety disorder (GAD) is a psychiatric condition where both physical and mental symptoms are observed due to the activation of the sympathetic system. It is known that the disorder affects the cardiovascular system. The present study aimed to analyze arterial stiffness in GAD patients and compare the findings with healthy controls.

Materials and Methods: 40 patients diagnosed with GAD and 40 healthy individuals were included in the study. Carotid and femoral artery intima-medial thickness (IMT) and arterial thickness parameters were measured with Doppler ultrasonography.

Results: The femoral IMT of the patients was significantly low. Although the carotid IMT was higher in patients when compared to the controls, the difference was not statistically significant. A significant negative correlation was determined between fluoxetine equivalent dose and femoral IMT. There was a correlation between femoral IMT and fluoxetine equivalent dose.

Conclusion: Arterial stiffness should be investigated for its potential to indicate cardiovascular risk in GAD. Further comprehensive studies should be conducted to clarify whether atherosclerosis symptoms were associated with the nature of the GAD or prescription medicine.

Keywords: Arterial stiffness, generalized anxiety disorder, cardiovascular risk, intima–media thickness.

Öz

Amaç: Yaygın anksiyete bozukluğu (YAB) sempatik sistemin aktive olmasıyla birlikte bedensel ve ruhsal belirtilerin bir arada görüldüğü psikiyatrik hastalıktır. Bu hastalıkta kardiyovasküler sistemin etkilendiği bilinmektedir. Bu çalışmada YAB tanılı hastalarda arter sertliğini değerlendirmeyi ve sağlıklı kontrollerle kıyaslamayı amaçladık.

Gereç ve Yöntem: YAB tanısı almış 40 hasta ve 40 sağlıklı birey çalışmaya dahil edildi. Karotis ve femoral arter intima-medial kalınlığı (IMT) ve arteriyel kalınlık parametreleri doppler ultrasonografi ile ölçüldü.

Bulgular: Hastaların femoral IMT değeri anlamlı şekilde düşük bulunmuştur. Hastalarda carotid IMT değeri ise sağlıklılardan daha kalın olmasına rağmen bu fark istatistiksel olarak anlamlı değildi. Fluoksetin eş değer dozu ile femoral IMT arasında negatif yönde anlamlı bir korelasyon belirlenmiştir. Femoral IMT ile fluoksetin eş değer dozu arasında ilişki olduğu görülmüştür.

Sonuç: Arteriyel sertlik YAB' da kardiyovasküler riski gösterebilme potansiyeli açısından araştırılmalıdır. Ateroskleroz belirtilerinin YAB hastalığının doğası gereği mi yoksa kullanılan ilaçlarla ilişkili mi olduğunu netleştirebilmek için daha geniş kapsamlı çalışmalara ihtiyaç bulunmaktadır.

Anahtar kelimeler: Arteriyrl sertlik, yaygın anksiyete bozukluğu, kardiyovasküler risk, intima–media kalınlığı

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INTRODUCTION

Generalized anxiety disorder (GAD) is a chronic disorder characterized by uncontrollable excessive anxiety, stress, and accompanying autonomic nervous system symptoms. In addition to cognitive and emotional anxiety symptoms, autonomic nervous system (ANS) symptoms, including tremors, hot flashes, palpitations, and sweating, are frequently observed, negatively affecting individual functions[1,2].

Anxiety pathophysiology entails a decrease in parasympathetic activity, deterioration of the neuroendocrine system, and increases in blood pressure and vascular resistance due to the overstimulation of the heart muscle and increased sympathetic activity[3]. High sympathetic activity leads to an increase in cortisol levels, dysfunction in platelets, higher leukocyte adhesion and aggression, and an increase in inflammatory cytokines. Furthermore, the proliferation of vascular smooth muscle cells is increased by the inhibition of the cholesterol uptake by macrophages, triggering atherosclerosis by cytokine release from lymphocytes and the development of adhesion molecules on endothelial cells[4]. The triggered neuroendocrine system insulin resistance could increase the metabolic syndrome risk, leading to obesity, type 2 diabetes, and hypertension risks[4].

Several studies have been conducted to investigate the correlations between diabetes, hypertension and coronary artery diseases, obesity and anxiety, and associated disorders that facilitate atherosclerotic background[5-8]. It has been suggested that an increase in anxiety levels could lead to metabolic syndrome, which is often accompanied by arterial stiffness[9]. In a study, where the correlation between coronary artery disease (CAD) and anxiety was investigated, and coronary angiography findings were classified, the anxiety levels of the participants in the group with abnormal findings were significantly higher when compared to the participants with normal findings, although the risk factors were similar. The study demonstrated that psychological factors could be an independent predictor of CAD in individuals with high anxiety and depression scores[10]. Especially GAD, panic disorder, and social phobia are common anxiety disorders in individuals with CAD. In a previous study, the rate of diagnosis with at least one anxiety disorder was 36% in individuals with CAD, and the lifetime diagnosis rate was 45.3%[11]. Furthermore, the severity of anxiety symptoms has been considered important not only in terms of the development of CAD but also that of a secondary cardiovascular problem[12].

Arterial stiffness is one of the important cardiovascular disease risk factors[13]. Ultrasonographic (USG) measurement of the outer arterial wall thickness allows the non-invasive detection of arterial stiffness and determination of wall elasticity[14]. Intima-media thickening (IMT) induced by endothelial dysfunction is an early sign of atherosclerosis. Arterial stiffness was described as a decrease in vessel elasticity. It is used in conjunction with distensibility and compliance in the analysis of vessel functions. Compliance is the capacity of the vessel to adapt (expand) to changes in pressure. Distensibility is the volumetric change during compliance. The measure of changes in vessel structure under pressure is elastic modulus. The increase in arterial stiffness leads to a decrease in the buffering ability of arteries, especially that of the carotid and femoral arteries, and deteriorates cardiac performance[15,16].

We considered that GAD affects arterial stiffness. The literature review revealed an inadequate number of studies that investigated arterial stiffness in GAD patients. We hypothesized that atherosclerosis and cardiovascular pathologies that could accompany GAD, which is quite prevalent in society, could be identified with ultrasonography, a simple and inexpensive method. Thus, we aimed to analyze arterial stiffness in GAD, which is associated with diseases that induce atherosclerosis, and to predict cardiovascular risks in these patients.

MATERIALS AND METHODS

Participants

The Fırat University, School of Medicine ethics committee approved the current study (date:04.11.2021, no:2021/11-37). The present study was conducted in compliance with the ethical standards prescribed in the Declaration of Helsinki and consent was obtained from the participants. While calculating the sample of the study, the G*Power 3.1.9.2 program was used and the "Evaluation of arterial stiffness in patients with schizophrenia" study was taken as a reference. Accordingly, it was determined that at least 60 participants, at least 30 in the patient group and 30 in the control group, should be reached with a confidence interval of 95% and a power of 80%

(Effect size= 0.7379179). The study was conducted with 48 patients who presented to the Psychiatry Department of Elazığ Fethi Sekin City Hospital, diagnosed with GAD based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and met the study criteria, and 40 healthy controls without any mental disorder. Eight patients subsequently dropped out of the study due to personal reasons. Inclusion criteria included GAD diagnosis between the ages of 18 and 50, absence of a known metabolic disease, physical pathology or neurological disease, other mental disorder, and no additional medication other than the current psychiatric treatment. The control group members were individuals between the ages of 18 and 50 (due to the increased risk of atherosclerosis in advanced age) without psychiatric, metabolic, and neurological diseases and drug use. The control group consisted of volunteer hospital staff and patient relatives. Both the medical history files of these individuals were examined and their mental status examinations were performed by the same psychiatrist.

Participants with a known history of alcohol and substance abuse disorder, metabolic syndrome, hypertension, hyperlipidemia, diabetes, cardiovascular disease, nephrological disease, peripheral artery disease comorbidities, and drug use for these reasons were excluded from the study. Since arterial stiffness may increase with age[17], participants over 50 were not included in the study.

Procedure

The present study was conducted at Elazığ Fethi Sekin City Hospital Psychiatry Department between January and September 2022. After the participants signed written consent, their sociodemographic data were collected, routine whole blood and biochemistry tests were requested, and weight-height, systolic, and diastolic arterial blood pressure (SBP, DBP) of the participants was measured. Then, the arterial thickness was measured by a radiologist with Doppler ultrasonography (USG). The measurements were made by the same radiologist each time.

Hemogram and general biochemistry tests (fasting blood glucose, sodium, potassium, chloride, magnesium, calcium, creatinine, triglyceride, HDL, LDL, total cholesterol, aspartate aminotransferase, alanine aminotransferase, etc.) were requested, and subjects with certain pathological parameters (fasting blood glucose >100), triglyceride >150 mg/dl, high-density lipoprotein <40 mg/dl in men and <50 mg/dl in women, low-density lipoprotein >130 mg/dl, total cholesterol > 220 mg/dl, creatinine >1.40 mg/dl in men and >1.30 mg/dl in women) were excluded from the study[18].

Systolic and diastolic blood pressures of all participants were measured with a manual sphygmomanometer in the sitting position, and those with SBP >130 mm/Hg and DBP >80 mm/Hg in at least 3 measurements at 10-minute intervals were excluded from the study[18].

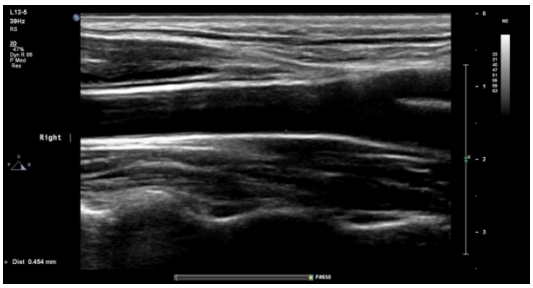

Figure 1. Intima-medial thickness (IMT) measurement approximately 1 cm before the right CCA artery bifurcation.

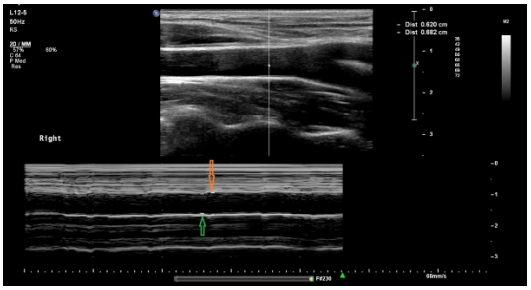

Figure 2. Measurement of systolic (orange arrow) and diastolic (green arrow) diameter on the right CCA artery.

Furthermore, the waist circumference of the participants was measured manually with a tape measure, males with a waist circumference of over 102 cm and females with a waist circumference of over 88 cm, and those with BMI>30 kg/m2 (body mass index) were excluded from the study[18]. The antidepressant doses taken by the patients were converted to fluoxetine equivalent doses with a dose equivalency method for standardization[19].

USG technique

A high-resolution Doppler USG device (Philips Affiniti 50 G, L 12-5 Mh linear probe) was employed.

Right femoral artery measurements were obtained when the patient was in the supine position, and right carotid artery measurements were obtained while the neck was hyperextended. Intima-media thickness (IMT) was measured at approximately 1 cm anterior of the right CCA artery bifurcation (Figure 1). Systolic and diastolic diameters were measured at the right CCA artery (Figure 2).

Arterial thickness parameters were calculated with the following formulas as described in the literature[16].

-Cross-sectional compliance = (π (SD^2-DD^2))/(4.$\triangle$P)
-Cross-sectional distensibility = (SD^2-DD^2)/(DD^2.$\triangle$P)
-Diastolic wall stress = (DD/(2.IMT)).((SP + SD)/2)
-Elastic modulus = (3/(1+(Cross-sectional area of lumen / Cross-sectional area of wall)) / Cross-sectional distensibility

Statistical analysis

Statistical analyzes were conducted on SPSS v.22 software (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). In the study, categorical descriptive data are presented as count and percentages, and continuous data are presented as mean ± standard deviation (Mean±SD). Chi-square analysis (Pearson Chi-square) was employed to compare categorical variables between the groups. The conformity of continuous variables to normal distribution was determined with the Kolmogorov-Smirnov test. Paired group data with normal distribution were compared with Student's t-test, and Mann Whitney U test was used for the data without normal distribution. The Pearson correlation test was employed for normally distributed data, and the Spearman correlation test was used for the data that did not exhibit a normal distribution. Linear regression analysis was conducted to determine the predictor of the dependent variable. While creating the model, it was included in the model that was significant in the correlation analysis, and the Enter method was used. The statistical significance level was accepted as $p<0.05$ in the analysis.

RESULTS

A total of 80 participants, including 40 patients and 40 controls, were included in the study. The mean age was 34.1±10.4 in the patient group and 34.0±7.5 in the control group, and there was no significant difference between the mean group ages (p=0.961). 52.5% of the patient group were female and 47.5% were male, 55% of the control group were female and 45% were male, and there was no significant difference between the groups based on gender (p=0.370). There was no significant difference between the patient and control groups based on other parameters (p>0.05) (Table 1).

Table 1. Comparison of patient and control group demographics

		Patient		Control		p*
		n	%	n	%	
Age, Mean ± SD		34.1±10.4		34.0±7.5		0.961**
Gender	Female	21	52.5	22	55.0	0.823
	Male	19	47.5	18	45.0	
Marital status	Unmarried	21	52.5	17	42.5	0.370
	Married	19	47.5	23	57.5	
Education	Middle school or lower	20	50.0	12	30.0	0.162
	High school	12	30.0	19	47.5	
	College	8	20.0	9	22.5	
Residence	Township	16	40.0	18	45.0	0.651
	Urban center	24	60.0	22	55.0	
Income	Low	15	37.5	13	32.5	0.885
	Medium	19	47.5	20	50.0	
	High	6	15.0	7	17.5	
Employment	Yes	18	45.0	21	52.5	0.502
	No	22	55.0	19	47.5	
Smoking	Yes	20	50.0	18	45.0	0.654
	No	20	50.0	22	55.0	
Mental disorders in the family	Yes	7	17.5	6	15.0	0.762
	No	33	82.5	34	85.0	

Self-mutilation	Yes	5	12.5	4	10.0	0.723
	No	35	87.5	36	90.0	
Suicide	Yes	3	7.5	1	2.5	0.615
	No	37	92.5	39	97.5	
Medication	Antidepressant	21	52.5	-		-
	Benzodiazepine	5	12.5			
	Multiple	14	35.0			
Fluoxetine equivalent dose, Mean±SD		30.2±10.7		-		-

*Chi-square analysis, **Student t test.

Table 1. Comparison of patient and control group BMI, blood pressure, and arterial pressure

	Patient	**Control**	**p**
	Mean±SD	Mean±SD	
BMI	24.7±2.3	23.3±2.5	**0.014***
Systolic pressure	117.6±10.3	114.2±9.2	0.067**
Diastolic pressure	70.5±8.8	70.8±6.0	0.980**
Carotid IMT	.51±.14	.50±.08	0.409**
Carotid Compliance	.16±.05	.16±.08	0.547**
Carotid Distensibility	.008±.012	.006±.003	0.749**
Carotid Diastolic Wall Stress	381.7±85.0	373.8±87.0	0.832**
Carotid Elastic Modulus	152.3±81.0	151.4±99.4	0.788**
Femoral IMT	.42±.10	.45±.08	**0.045****
Femoral Compliance	.18±.11	.17±.09	0.863*
Femoral Distensibility	.005±.003	.004±.002	0.722**
Femoral Diastolic Wall Stress	516.7±130.2	465.7±106.0	0.063**
Femoral Elastic Modulus	164.7±102.9	168.1±93.8	0.459**

*Student t-test, **Mann Whitney U test; BMI: Body Mass Index, IMT: Intima-Media Thickness

Table 3. Correlations between fluoxetine equivalent dose and diagnosis time and other variables

	Fluoxetine equivalent dose	
	r	p
Age	.014*	.934
Psychiatric diagnosis period	.026*	.874
Duration of psychotropic drug use	.070*	.666
BMI	-.181**	.265
Systolic pressure	.084*	.605
Diastolic pressure	.008*	.959
Carotid IMT	-.124*	.445
Carotid Compliance	.197*	.223
Carotid Distensibility	-.056*	.733
Carotid Diastolic Wall Stress	.009*	.957
Carotid Elastic Modulus	-.212*	.188
Femoral IMT	**-.444***	**.004**
Femoral Compliance	-.054**	.742
Femoral Distensibility	.057*	.727
Femoral Diastolic Wall Stress	.224*	.165
Femoral Elastic Modulus	-.163*	.316

BMI: Body Mass Index, IMT: Intima-Media Thickness; *Spearman correlation, **Pearson correlation

Table 4. Linear regression analysis of factors associated with drug equivalent

	β	SE	Standard β	t	p
Fluoxetine equivalent dose (R^2=0.210; F=4.913; p=0.013)					
BMI	-.536	.689	-.115	-.778	.442
Femoral IMT	-46.919	16.287	-.426	-2.881	**.007**

BMI: Body Mass Index, IMT: Intima-Media Thickness

BMI (p=0.014) of the patient group was significantly higher when compared to the control group, and femoral IMT (p=0.045) was significantly lower (Table 2). A negative and significant correlation was determined between fluoxetine equivalent dose and femoral IMT (Table 3).

The multiple linear regression analysis revealed that femoral IMT predicted fluoxetine equivalent dose. In this case, there was a correlation between Femoral IMT and fluoxetine equivalent dose (β=46.919; p=0.007) (Table 4).

DISCUSSION

In the present study, the femoral IMT, an arterial stiffness parameter, was significantly lower in GAD patients when compared to the healthy controls. Although the carotid IMT was also higher in patients when compared to healthy controls, the difference was not statistically significant. It is known that subclinical cardiovascular changes do not affect all arterial beds similarly and simultaneously. This could be due to the differences in the composition of the vascular wall, namely muscular arteries (e.g., the femoral artery), elastic arteries (e.g., the carotid artery), and the location of the arteries[20]. There was no significant correlation between carotid atherosclerosis and the severity of anxiety symptoms. This was consistent with the findings of the study where no significant correlation was reported between depressive and anxiety disorders and carotid atherosclerosis[21].

In a study conducted on 449 lifelong depressive and/or anxiety disorder cases and 169 healthy controls, it was reported that the arterial stiffness parameters were significantly higher in the patient group; however, the current study findings revealed no difference between arterial distensibility across the groups, suggesting that exposure to depression and anxiety could facilitate the development and progression of atherosclerosis and other cardiovascular conditions[22]. Arterial stiffness was found to be increased in 42 patients diagnosed with panic disorder, whose arterial stiffness was measured by carotid-femoral pulse wave velocity (CF-PWV) measurement, compared to the healthy control group, and it was shown that the risk of cardiovascular disease was higher[23]. In another study, it was reported that the current major depressive episode acutely exacerbated arterial stiffness in women; however, arterial stiffness was reversible with timely and effective antidepressant treatment[24]. In a study that investigated the effects of SSRIs on proinflammatory cytokines in first-attack GAD patients, moderate acute anti-inflammatory effects of SSRIs were demonstrated in GAD, and it was reported that these anti-inflammatory effects were due to the anxiolytic effects of SSRIs[25].

In another study, significantly higher IMT was reported in schizophrenia patients; however, there was no significant difference between the arterial stiffness of the patient and control groups. The authors stated that this could be explained by the potential protective impact of antipsychotic treatment on arterial stiffness[26]. It was suggested that this could be due to the reduction in blood pressure by the antipsychotic drugs and the anti-inflammatory properties of the latter[27,28]. Antidepressant drugs also affect blood pressure similar to antipsychotic drugs[29]. Although certain studies argued that antidepressants could lead to hypertension[30], it is known that antidepressant drugs generally lower blood pressure[31]. In a study where the cardiovascular effect of citalopram was investigated in 811 elderly depression patients, it was concluded that the antidepressant could reduce sympathoadrenal hyperactivity and increase cardiovascular morbidity[32]. Although it was reported that tricyclic antidepressant drugs were associated with high inflammation[33], Miller et al.[34] demonstrated that antidepressant drugs, especially serotonin reuptake inhibitors, reduced inflammation. High inflammation could lead to degenerative pathological changes in the arterial wall, increasing arterial stiffness and cardiovascular risks[35]. In the current study, femoral IMT, an arterial stiffness parameter, was found to be lower in the patient group when compared to the healthy

controls. This suggested that although the patient group was expected to have an increased atherosclerosis risk due to inflammation induced by the disease, GAD patients had a lower cardiovascular disease risk due to antidepressant treatment. In the present study, a negative and significant correlation was determined between fluoxetine equivalent dose and femoral IMT, supporting our hypothesis. Wong et al.[36] reported that successful antidepressant treatment improved hemorheological stress-hemoconcentration measures that contributed to high cardiovascular disease risk and attenuated the progression of atherosclerotic plaque in the arteries by improving major depressive disorder symptoms. Also, due to their effects on platelet activation and atherosclerosis, serotonin reuptake inhibitors were determined to function as safe and effective agents against the development and prognosis of coronary heart disease[37]. However, Camocha et al.[38] did not support the correlation between antidepressants and subclinical atherosclerosis, including carotid intima thickness.

The strength of the current study was the measurement of arterial stiffness with ultrasonography, an inexpensive and easy method, in GAD patients. Furthermore, predisposal factors to atherosclerosis such as cardiovascular disease history, hypertension, hypercholesterolemia, metabolic syndrome, and diabetes mellitus were excluded in the present study.

Study limitations included the small sample size, the fact that certain GAD patients were under drug treatment (these patients were in clinical partial remission while on treatment) certain participants smoked and used alcohol, and the lack of similar body mass index across the patient and control groups.

In conclusion, arterial stiffness induced by femoral IMT was lower in GAD patients when compared to healthy controls. Although the carotid IMT was thicker in the patient group, the difference was not statistically significant. The femoral IMT decreased significantly in the patient group with the increase in the fluoxetine equivalent dose. The current study laid the groundwork for future studies to clarify whether this was due to the nature of the disease or antidepressant treatment. Arterial stiffness should be investigated in GAD to evaluate cardiovascular risks. Further studies with repeated measurements of arterial stiffness parameters are required to identify and confirm arteriosclerosis in this patient group.

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