Original Paper

DOI: 10.5455/bcp.20160325085828

Severity of Depression and Anxiety Symptoms is Associated with Increased Arterial Stiffness in Depressive Disorder Patients Undergoing Psychiatric Treatment

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ABSTRACT:

Severity of depression and anxiety symptoms is associated with increased arterial stiffness in depressive disorder patients undergoing psychiatric treatment

Objective: Depression and anxiety are associated with both subclinical and clinical cardiovascular disease. Endothelial dysfunction, atherosclerosis, and inflammation are some of the underlying mechanisms. Pulse wave velocity (PWV) and augmentation index (AIx) are noninvasive markers for evaluation of arterial stiffness. The aim of this study was to examine the association between arterial stiffness parameters and depression/ anxiety scores in depressive patients undergoing psychiatric treatment.

Methods: The study population consisted of 30 patients with depression undergoing psychiatric treatment at least 4 weeks, and 25 age and gender matched healthy controls. Depression and anxiety were assessed by self-reported scales, including the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). Measurements of arterial stiffness parameters were performed by using a Mobil-O-Graph arteriograph system, which detects signals from the brachial artery.

Results: Baseline characteristics and clinical data were similar between the two groups. BDI and BAI scores were statistically significantly higher in patients with depression ($p<0.001$, $p<0.01$). PWV and AIx were statistically significantly higher in patients with depression compared to controls (6.40±1.31 m/s vs 5.51±0.41 m/s and 26.9±12.1 % vs 17.4±11.3 %, $p=0.001$, $p=0.004$, respectively). PWV and AIx positively, mildly and statistically significantly correlated with BDI and BAI scores.

Conclusion: Arterial stiffness parameters were statistically significantly higher in depressive patients receiving antidepressant treatment. Moreover, arterial stiffness parameters statistically significantly correlated with BDI and BAI. Assessment of arterial stiffness parameters may be useful for early detection of cardiovascular deterioration in depressive patients undergoing antidepressant treatment.

Keywords: arterial stiffness, pulse wave velocity, augmentation index, depression, anxiety

Klinik Psikofarmakoloji Bulteni - Bulletin of Clinical Psychopharmacology 2016;26(3):287-93

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Date of submission:
January 19, 2016

Date of acceptance:
March 25, 2016

Declaration of interest:
O.Y., M.S., E.D., T.K., Z.S., N.S., G.K., S.E., I.S., K.S.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Cardiovascular comorbidities are challenging in psychiatry practice[1] and arterial stiffness (AS) is an overlooked issue that might be an important surrogate marker for cardiovascular morbidity and mortality[2,3]. The relationship between depression and anxiety with overt/ subtle cardiovascular problems is well established in the literature[4-7]. A recent meta-analysis showed that the presence of depression was not only an independent predictor of cardiovascular disease (CVD) but also played an important role in prognosis. A relative risk of future coronary artery disease in patients who have depressive symptoms has been provided in a meta-analysis of 11 prognostic studies (OR=1.81, 95% CI

1.53-2.15)[8]. Interestingly, healthy young people with family history of depression were shown to have increased blood pressure and arterial stiffness[9]. In addition, lower cardiovascular fitness at age 18 was related to the development of significant depression in the adulthood (HR= 1.96, 95%, CI 1.71-2.23). Decreased cardiovascular fitness in males who enlisted for military service has been a predictive factor for future depression, thus the association between depression and CVD seems bidirectional[10]. Although the relationship between depression and CVD is unclear in terms of which one triggers another one, previous studies have shown that there is a close relationship between endothelial dysfunction, atherosclerosis, and depression[11-13].

Inflammation is another important entity in pathophysiology of cardiovascular disease and depression. Recently, Sunbul et al. reported an association with systemic inflammation and increased arterial stiffness parameters in patients with psoriasis[14]. The elevated pro-inflammatory cytokines such as; interleukin-6 (IL-6) and factor-α (TNF-α) and IL-1B have been demonstrated in patients with major depressive disorder[15,16]. Platelet activating factors (PAFs) those are family of potent pro-inflammatory phospholipids were related with depressive symptoms in coronary artery disease[17]. Thus inflammation may be an important underlying mechanism of increased arterial stiffness in patients with depressive disorder.

Assessment of arterial stiffness parameters is a non-invasive method of subclinical CVD and arterial aging[18]. Pulse wave velocity (PWV) and augmentation index (AIx) are non-invasive markers for assessment of arterial stiffness[19]. Mc Eniery et al. demonstrated that PWV and AIx correlated with endothelial dysfunction[20]. Therefore, assessment of arterial stiffness parameters may help the clinician to evaluate increased risk of CVD in patients with depression. The aim of this study was to examine the association between arterial stiffness parameters and depression/ anxiety scores in depressive patients who were undergoing treatment.

METHODS

Study Population

The study was conducted between October-December 2013 in psychiatry outpatient clinics of Marmara University Education and Research Hospital. The sample size was calculated by power analyses consistent with the literature[21] and we included thirty consecutive patients to our study. Patients with depressive disorder according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, Revised Text (DSM IV, TR; APA 2000) and 25 age-sex similar healthy controls were enrolled in the study. The exclusion criteria were as follows: i) age < 18 and >65 years, ii) being illiterate, iii) having extra-cardiac risk factors such as past or current hypertension (systolic and/ or diastolic blood pressure ≥140/90 mmHg), diabetes mellitus (fasting plasma glucose levels more than 126 mg/dL in ≥3 measurements), hyperlipidemia (serum total cholesterol ≥200 mg/dl, serum triglyceride ≥150 mg/dl, low-density lipoprotein cholesterol ≥130 mg/dl) or use of antihypertensive, antidiabetic or lipid-lowering medication, iv) history of nicotine, alcohol or substance abuse/ dependence, v) using antidepressant medication insufficient period (under 4-8 week) for the treatment. According to APA (American Psychiatric Association) treatment guideline, it is suggested to wait at least 4 to 8 week for the treatment response in patients with depressive disorder using antidepressant treatment[22]. Thus, we included the patient group in this period into our study and excluded the patients taking antidepressant treatment under four weeks. Written informed consents were obtained from each patient prior to the study. The study was performed in accordance with the principles stated in the Declaration Criteria of Helsinki and approved by the Local Ethics Committee.

Evaluation of Arterial Stiffness Parameters

Prior to study all attendants refrained from eating and drinking alcohol, coffee, or tea for at least 12

hours. Arterial stiffness test was performed in the supine position in a quiet, temperature-controlled room (22-24°C) between 08.00-10.00 a.m. Measurements were performed by using a Mobil-O-Graph arteriograph system (Mobil-O-Graph NG, Stolberg, Germany). In this system signals are detected from brachial artery although cuff pressure is 35 mmHg higher than systolic pressure in the brachial artery. Arterial stiffness depends on the fact that the contraction of the myocardium initiates a pulse wave (early systolic peak) running down in the aorta. At the distal branching point first wave is reflected from the aortic wall and leads to a reflected second wave (late systolic wave). The morphology of second reflected wave based on the stiffness of the large artery. Aix (AIx adjusted for heart rate 75 bpm) and PWV are calculated according to current guidelines by the way of amplitude and time difference of first and second wave[23].

Self-Report Questionnaires

After a brief socio-demographic questionnaire, all participants were asked to fill out Beck Depression and Beck Anxiety Inventories.

Beck Depression Inventory (BDI) is a 21-item survey that measures factors related to the affective (e.g., hopelessness, irritability, cognitive problems, feelings of guilt or being punished) and somatic (e.g., fatigue, weight loss, and loss of sexual desire) components of depression. Validity and reliability study of BDI for adaptation to the Turkish language has been performed and the cut-off value for BDI scores was considered as 17 points[24,25].

Beck Anxiety Inventory (BAI) intervals are <7 points minimal anxiety, 8-15 points mild anxiety, 16-25 points moderate anxiety, and 26-63 points severe anxiety[26]. Validity and reliability study of BAI for adaptation to the Turkish language has been conducted[27].

Statistical Analysis

Statistical analyses were performed using SPSS 16.0 statistical package for Windows (SPSS Inc., Chicago, IL). Continuous data were expressed as mean±standard deviation while categorical data were presented as percentage. Chi-square test was used for comparison of categorical variables while student T-test or Mann-Whitney U test were used to compare parametric and nonparametric continuous variables, respectively. Normal distribution of data was assessed by Kolmogorov-Smirnov test. Correlation analysis was performed by Pearson's (normal distribution) or Spearman's rank correlation (non-normal distribution) test. A value of $p<0.05$ was considered statistically significant.

RESULTS

The study population consisted of 30 patients with depressive disorder and 25 age and gender matched healthy controls. Baseline characteristics

Table 1: Baseline characteristics and clinical data of the study population

	Patient with depression (n=30)	Control group (n=25)	p
Age, years	39.4±10.5	35.5±7.5	0.176
Female Gender, n	22	16	0.456
BDI Scores	30.0±9.7	5.9±5.2	<0.001
BAI Scores	29.7±13.3	6.3±3.6	<0.001
Drug treatment	17		
SSRI, n	17	-	-
SNRI, n	5		
SSRI+SGA, n	4		
SSRI+NASSA, n	4		

*Data are presented as mean ± standard deviation or number of patient.
BAI: Beck anxiety inventory, BDI: Beck depression inventory, NASSA: Noradrenergic and specific serotonergic antidepressant, SGA: Second generation antipsychotics, SNRI: Serotonin noradrenalin reuptake inhibitors, SSRI: Selective serotonin reuptake inhibitors.

and clinical data were shown in Table 1. BDI and BAI scores were statistically significantly higher in patients with depression. The classes of drugs that the patients received were as follows: selective serotonin reuptake inhibitors (SSRI, n=17), serotonin noradrenalin reuptake inhibitors (SNRI, n=5), SSRI + second generation antipsychotics (n=4) and SSRI + noradrenergic and specific serotonergic antidepressants (n=4).

While peripheral systolic blood pressure was statistically significantly higher in depressive patients (p=0.006), other cardiac hemodynamic parameters were similar between two groups. We also evaluated arterial stiffness parameters between the two groups. Comparison of cardiac hemodynamic parameters was shown in Table 2.

While peripheral systolic blood pressure was statistically significantly higher in depressive patients (p=0.006), PWV and AIx were statistically significantly higher in patients with depression compared to controls [6.0 (5.0-9.9) vs 5.5 (5.0-6.2) and 26.9±12.1 vs 17.4±11.3, p= 0.001, p=0.004, respectively] (Figure 1,2). Arterial stiffness parameters were statistically significantly higher in depressive patients receiving antidepressant treatment. Moreover, arterial stiffness parameters statistically significantly correlated with BDI and BAI. Patients with depression had statistically significantly higher BDI (p<0.001) and BAI scores (p<0.001) compared to healthy controls. Correlation analysis revealed that there were positive, mild, statistically significant correlations

Table 2: Comparison of cardiac hemodynamic parameters of study population

	Patients with depression (n=30)	Control group (n=25)	p
Peripheral Systolic Blood Pressure (mmHg)	122.5 (104.0-149.0)	114.0 (102.0-140.0)	0.006
Peripheral Diastolic Blood Pressure (mmHg)	77.7±12.5	76.1±9.6	0.606
Peripheral Mean Blood Pressure (mmHg)	98.3±9.4	93.9±7.6	0.064
Peripheral Pulse Pressure (mmHg)	42.0 (23.0-94.0)	38.0 (21.0-64.0)	0.084
Heart Rate (beat/min)	81.3±13.2	75.6±10.0	0.077
Cardiac Output (l/min)	4.2±0.5	4.1±0.5	0.299
Cardiac Index (l/min*1/m^2)	2.3±0.4	2.3±0.4	0.906
Central Systolic Blood Pressure (mmHg)	111.7±10.8	106.8±6.6	0.054
Central Diastolic Blood Pressure (mmHg)	79.4±11.9	77.6±9.7	0.547
Central Pulse Pressure (mmHg)	32.3±9.9	29.2±7.7	0.208
Reflecting Magnitude (%)	62.0 (39.0-75.0)	66.0 (41.0-77.0)	0.270

*Data are presented as mean ± standard deviation or median (minimum-maximum)

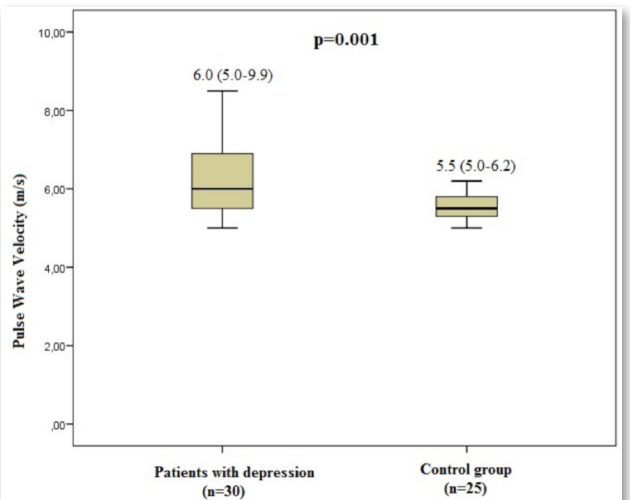

Figure 1: Pulse Wave Velocity is significantly higher in depression patients compared to controls

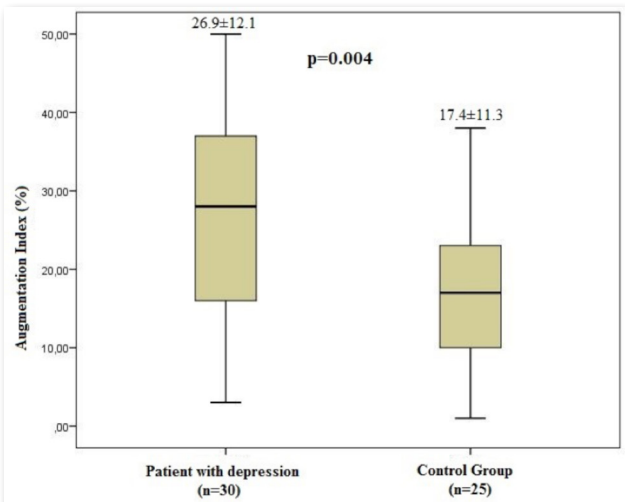

Figure 2: Augmentation index is significantly higher in depression patients compared to controls.

Table 3. Correlation of Beck Depression Inventory and Beck Anxiety Inventory with arterial stiffness parameters

Arterial Stiffness Parameters	Beck Depression Inventory		Beck Anxiety Inventory	
	r	p	r	p
Pulse Wave Velocity (m/s)	0.384	0.004	0.325	0.015
Augmentation Index (%)	0.311	0.021	0.384	0.004

between arterial stiffness parameters and BDI and BAI scores (Table 3).

DISCUSSION

In this study, we demonstrated a significant increase of PWV and AIx in patients with depression compared to healthy controls. Moreover, arterial stiffness parameters were significantly correlated with depression and anxiety scores. Previous studies have shown that presence of depression increases the risk of CVD and the existing of CVD also increases the risk of depression[28,29]. In a study, higher values of PWV and AIx were of border significance in elder depressive patients[30], and statistically significant association between PWV with depressive disorder has been reported[13] which is in line with our findings. In addition, in a recently published well-designed study, the authors have compared 449 cases with lifetime diagnoses of depressive and/ or anxiety disorder and 169 healthy controls for PWV and AIx[5]. Similar to our findings, they found significant increase in AIx in patients with depressive and/ or anxiety disorder. Interestingly, the PWV was also shown to be increased in female patients with depression[31]. Progressive loss of arterial elasticity is related to stroke, left ventricular hypertrophy and possible heart failure and predisposition to vessel wall damage[32]. Moreover, AIx might be correlated with endothelial dysfunction[20]. Thus, considering the above-mentioned findings, we suggested that depressive patients might have clinically occult endothelial dysfunction. In a previous study, the severity and duration of depressive symptoms were positively correlated with increase in AIx[5]. In another study, a positive correlation between symptom severity of depression and PWV was detected in adolescent patients with major depressive disorder (age between 16-21 years, n=157)[18].

It can be argued that whether antidepressant treatment and/ or decrease in depressive symptom severity or drug specific effects have influences on arterial stiffness or not as measured by PWV and AIx. In a study in older adults with depression (n=75), after one year of treatment, duloxetine (60 mg/d) but not escitalopram (10 mg/d) was shown to be related with an increase in PWV that was suggested as drug specific effect by the investigators[33].

Oulis et al. have found that antidepressant treatment in drug free women patients with depression (n=20) is related with decrease in arterial stiffness upon timely and effective treatment[31]. And also they demonstrated that full responders had significantly greater vascular improvement[31]. Although we could not compare the arterial stiffness parameters between pretreatment and undergoing treatment periods due to lack of pretreatment scores of patients, we demonstrated that only medical treatment do not prevent from worsening the stiffness parameters in depressive patients compared to healthy control group. The worsening of stiffness parameters may be related to higher depression and anxiety scores in the patients group than healthy controls. Thus, we considered that symptom severity might also contribute to increased arterial stiffness in these patients despite being undergoing treatment.

Study Limitations

This study has several limitations. First, the relatively small sample size is important while interpreting our findings. The cross sectional design of the study might be a second limitation. It

would be better including medication naive patients into our study rather than healthy control group. Finally, lacking of knowledge about the duration of depressive illness is an important limitation. The antidepressant class in the current study is not homogenous that might confound the findings of high PWV and AIx. Finally, we did not evaluate the prognostic value of the arterial stiffness parameters and its relationship with the use of psychotropic medication. If we had followed a group of medication-naive depression patients with antidepressants, it would have been better to explain the differential effect of antidepressant drugs on arterial stiffness.

CONCLUSIONS

We demonstrated that arterial stiffness parameters were significantly higher in patients with depression those were receiving antidepressant treatment compared to healthy controls. Moreover, arterial stiffness parameters significantly correlated with BDI and BAI scores. Assessment of arterial stiffness parameters may be useful for early detection of cardiovascular deterioration in depressive patients undergoing medical treatment. Further prospective studies are needed to explore the relationship between arterial stiffness and medication-naive depression patients.

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