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Relationships between Depressive Symptoms and Endothelial Function Among Outpatients of a General Hospital in China

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Statistical Analysis C
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Manuscript Preparation E
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Background: This study aimed to investigate the endothelial function by reactive hyperemia index (RHI) in patients with depression, subjects recovering from depression, and subjects without a history of depression.

Material/Methods: Outpatients were recruited from a general hospital in China; 62 patients diagnosed with depression and the 17-item Hamilton Rating Scale for Depression (HAMD17) total scores ≥17 were enrolled as the depression group, 62 patients with a history of depression, discontinuation of antidepressants therapy at least 3 months ago, and HAMD17 ≤7 were recruited as remission group, and 62 subjects without a history of depression served as the control group (HAMD17 ≤7).

Results: The mean RHI was 1.93, 2.34, and 2.19 in depression, control, and remission groups, respectively, showing a significant difference among the 3 groups (P=0.0004). In addition, a marked difference in RHI was found between depression and control groups (P=0.0003) and between depression and remission groups (P=0.0270). However, there was no significant difference between remission and control groups (P=0.3363).

Conclusions: There is a relationship between depression and endothelial dysfunction in outpatients from a general hospital in China. The improvement of depression is synchronous with the improvement of endothelial function.

MeSH Keywords: Cross-Sectional Studies • Depression • Endothelial Cells • Remission Induction

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Background

Increasing clinical epidemiologic studies revealed that some common chronic diseases (such as coronary heart disease [CHD], diabetes mellitus [DM], and cerebral infarction [CI]) are closely associated with depression, and they were reciprocally causative and had an interaction [1–4]. To the best of our knowledge, the mechanisms underlying the concomitant depression in patients with chronic diseases are usually ascribed to the disruption of the hypothalamic-pituitary-adrenal (HPA) axis and the involvement of varieties of proinflammatory cytokines. In the past decade, some investigators proposed the concept of vascular depression [5]. Depression may not only be a result of vascular diseases, but also a risk factor of vascular diseases. The relationship between depression and vascular endothelial dysfunction (a feature in the early stage of vascular diseases) is currently an important research area [6].

According to embryology, vascular cells compose a barrier between the vascular wall and deep tissues. Further studies revealed that endothelial cells also have endocrine characteristics and are able to regulate inflammatory reactions and coagulation. Endothelial dysfunction is mainly characterized by endothelium-dependent diastolic dysfunction, which is ascribed to the reduction in nitric oxide (NO) production. Currently, 2 methods are employed to detect endothelial function: intravascular injection of acetylcholine and pressurization with a cuff. In terms of intravascular injection of acetylcholine, when the endothelial function is normal, acetylcholine may induce the vascular dilation via NO pathway; however, when the endothelial dysfunction is present, vasoconstriction occurs after injection of acetylcholine [7,8]. Although this method is regarded as the criterion standard for evaluating endothelial function, it is not widely used in clinics because it is invasive, time-consuming, and expensive. When pressurization with a cuff is used to block the blood flow of the brachial artery, rapid blood flow after deflation may cause a high shear stress to the endothelial cells and induce them to release NO, resulting in vascular dilation. Then, the flow-mediated dilation is measured to evaluate the endothelial function [9,10]. This method may be influenced by many factors and highly dependent on the level of detection ability, which results in low repeatability and reliability. EndoPAT is a peripheral arterial tonometry in which the change in the finger arterial pulse volume is measured to evaluate the endothelial function by reactive hyperemia peripheral arterial tonometry index (RHI) [10,11]. It has no disadvantages related to the above mentioned methods and can be widely applied in clinical practices.

A recent meta analysis [12] showed that both severe and transient depression were related to endothelial dysfunction. However, whether the endothelial function becomes normal or is still abnormal during the following remission of depression or even complete recovery from depression is still unclear (that is endothelial function and depression status are independent characteristics or mutually dependent) [13–16]. This may be ascribed to the fact that the vascular endothelial dysfunction is influenced by a variety of factors such as lifestyle, concomitant diseases, and pharmacotherapy. Studies have been conducted to investigate the endothelial function in patients who have recovered from depression by undergoing anti-depression therapies [13,17]. However, these studies focused on the influence of antidepressant treatment on endothelial function. Few studies have been conducted to investigate the relationship between endothelial function and depression recovery after excluding the influence of antidepressants.

We hypothesized the following: depression is closely related to endothelial dysfunction; the remission of depression symptoms is accompanied by the improvement of endothelial function; and that the endothelial function is worst in depression patients, best in non-depression patients, and moderate in remission patients.

Material and Methods

Subjects and setting

Patients were consecutively recruited from the Cardiology, Neurology, Endocrinology, and Clinical Psychology Clinics of Beijing Chaoyang Hospital from March 2013 to June 2014. These patients were aged 30–70 years, and had the ability to provide consent and cooperate with the questionnaire survey.

Subjects for the 3 groups were matched for age (±3y) and body mass index (±1 kg/m^2) at a ratio of 1:1:1 and there were 62 subjects in each group. This cross-sectional study was approved by the Ethics Committee of Beijing Chaoyang Hospital. Informed consent was obtained from all subjects in this study.

Depression group: Depression was diagnosed according to the Chinese version of the Modified Structured Clinical Interview for DSM-IV diagnostic criteria for patient version [18] by 2 trained clinical psychiatrists. All patients were drug-naıve and in their first episode of illness (they experienced a depressive episode for the first time), and had 17-item Hamilton Rating Scale for Depression total scores (HAMD17) ≥17.

Remission group: Subjects had a self-reported history of physician-diagnosed depression, HAMD17 ≤7, and antidepressants had been discontinued for at least 3 months.

Control group: All healthy controls were interviewed with the Structured Clinical Interview for DSM-IV, non-patient version. They were free of depression, other psychiatric or neurological illnesses, history of head injury, and had HAMD17 ≤7.

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Exclusion criteria were: severe cardiovascular disease (massive myocardial infarction and coronary artery bypass), acute diseases in internal medicine (such as acute nerve deafness), severe mental disorders (schizophrenia and bipolar disorder), and cognition impairment.

Demographic characteristics

Demographics characteristics, including gender, age (in years), and smoking history, were obtained by self-report.

Physical examination and medical history

Height was measured using a wall-mounted stadiometer and weight was assessed by using calibrated electronic scales. Body mass index (BMI) was calculated as kg/m^2. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured on the left arm. Fasting glucose (FG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL), and self-reported history of physician-diagnosed diseases (such as CHD, DM and CI) were also recorded.

Depressive symptoms

Current depressive symptoms were determined with HAMD17 [19], which is the most common scale used for clinical evaluation of depression status. There are 17 items in this scale and each item is graded 0–4. HAMD17 ≥17 indicates severe depression, and HAMD17 ≤7 denotes no depressive symptoms. This scale has acceptable reliability and validity in medical samples.

Endothelial function

EndoPAT2000 (Itamar Medical, Caesarea, Israel) has been widely used to measure the endothelial function, which is a beat-to-beat plethysmographic recording of the finger arterial pulse-wave amplitude (PWA) with pneumatic probes [20,21]. A variety of clinical studies have confirmed that this technique is convenient and easy to handle and had good reliability and intraclass correlation coefficients (0.78) [20–27]. In addition, it also has high sensitivity and specificity. In detecting CHD, the sensitivity and specificity of this technique were as high as 80% and 85%, respectively [28].

Detection of endothelial function was done between 8 and 10 am. Patients were fasting and in supine position. A cuff was inflated to obstruct the blood flow of the brachial artery for 5 min, followed by deflation and subsequent vascular dilation. EndoPAT software (version 2.3.2) was employed to calculate the ratio of signal amplitude before flow obstruction to that after flow obstruction. Then, RHI was obtained. The higher the RHI was, the better the endothelial function.

Statistical analysis

The demographics and clinical characteristics were compared with analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. The linear regression model was used to analyze the effect of candidate covariates on RHI, and the candidate covariates included gender, age, BMI, SBP, DBP, FG, TC, HDL, LDL,TG, cardiovascular disease (yes/no), cerebrovascular disease (yes/no), and DM (yes/no). The affected factors on RHI were analyzed by mono-factor analysis. The general linear model was employed to compare RHI among the 3 groups after adjusting the covariates, and Bonferroni method was used for the correction of multiple comparisons among groups. A value of 2-tailed $P<0.05$ was considered statistically significant. Statistical analysis was performed with SAS 9.3.

Results

There were no significant differences in gender, age, BP, BMI, FG, LDL, HDL, TC, TG, or history of chronic diseases among the 3 groups (Table 1). Results showed that the demographics and clinical characteristics were comparable among three 3 groups and were matched for age and BMI.

The influence of 15 variables (e.g., gender, age, and clinical indicators of RHI) was analyzed by linear regression analysis (Table 2). The results showed that DBP, TG, CHD, and HAMD17 had significant effects on RHI ($P<0.05$).

In terms of distribution balance of all covariates, a general linear model was used to compare RHI among the 3 groups without adjustments. The mean RHI was 1.93, 2.34, and 2.19 in the depression, control, and remission groups, respectively (Figure 1). The difference of RHI among the 3 groups was statistically significant ($P=0.0004$). Compared with the controls (2.337±0.697), RHI was significantly lower in the depression group (1.931±0.535; $P=0.0003$). RHI in the remission group (2.194±0.426) was markedly higher than in the depression group ($P=0.027$). However, there was no significant difference between remission and control groups ($P=0.3363$).

Discussion

After matching for age and BMI, patients in the 3 groups had comparable demographics and clinical characteristics. These patients were not receiving anti-depressants therapy when the RHI was measured. The results showed that depression was closely related to endothelial dysfunction, and endothelial function should be improved as symptoms of depression were relieved. The endothelial function in patients with remission from depression was comparable to that in non-depression patients.

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Table 1. Demographics and clinical characteristics of subjects in three groups.

	Depression	Remission	Non-depression		P
Gender				χ^2=0.134	0.9352
N (missing)	62 (0)	62 (0)	62 (0)		
Male/N (%)	26 (41.94)	25 (40.32)	24 (38.71)		
Female/N (%)	36 (58.06)	37 (59.68)	38 (61.29)		
Age				H=0.0163	0.9919
X±SD	54.18±9.69	54.15±9.63	54.00±9.65		
Median	54.00	54.00	54.00		
Range	33–70	33–70	33–70		
BMI				H=0.0451	0.9777
X±SD	25.09±2.91	25.09±2.79	25.14±2.84		
Median	24.78	24.78	24.99		
Range	19.05–31.28	19.05–30.41	19.05–30.41		
SBP				H=0.1044	0.9492
X±SD	132.02±11.4	131.77±9.46	132.58±11.26		
Median	130.00	130.00	130.00		
Range	100–160	110–160	120–165		
DBP				H=2.5992	0.2726
X±SD	78.56±10.1	76.29±8.54	75.95±8.43		
Median	80	80	75		
Range	60–105	60–95	60–100		
FG				H=4.6247	0.0990
X±SD	5.47±0.96	6.02±1.38	6.08±3.03		
Median	5.33	5.77	5.49		
Range	3.74–8.06	4.08–11.5	4.08–7.17		
TC				F=0.30	0.7443
X±SD	4.71±1.11	4.59±0.91	4.71±0.81		
Median	4.75	4.65	4.73		
Range	1.18–7.8	1.33–6.7	3.02–6.62		
HDL				H=0.7283	0.6948
X±SD	1.26±0.47	1.28±0.33	1.30±0.49		
Median	1.23	1.25	1.25		
Range	0.41–3.96	0.69–2.56	0.58–4.57		

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Table 1 continued. Demographics and clinical characteristics of subjects in three groups.

	Depression	Remission	Non-depression		P
LDL				H=1.6991	0.4276
X±SD	2.65±0.79	2.62±0.69	2.49±0.62		
Median	2.58	2.62	2.55		
Range	0.75–5.55	0.75–4.21	1.42–3.93		
TG				H=0.2367	0.8884
X±SD	1.77±0.90	1.73±0.94	1.72±1.01		
Median	1.58	1.55	1.57		
Range	0.42–4.33	0.42–4.62	0.43–6.76		
CHD				χ^2=1,451	0.4841
N (missing)	62(0)	61(1)	62(0)		
No/N (%)	38(61.29)	42(68.85)	44(70.97)		
Yes/N (%)	24(38.71)	19(31.15)	18(29.03)		
CI				χ^2=1.787	0.4092
N (missing)	62(0)	61(1)	61(1)		
No/N (%)	46(74.19)	39(63.93)	45(72.58)		
Yes/N (%)	16(25.81)	22(36.07)	17(27.42)		
DM				χ^2=0.987	0.6105
N (missing)	61(1)	61(1)	62(0)		
No/N (%)	50(81.97)	47(77.05)	52(83.87)		
Yes/N (%)	11(18.03)	14(22.95)	10(16.13)		

BMI – body mass index (kg/m^2); SBP – systolic blood pressure (mmHg); DBP – diastolic blood pressure (mmHg); FG – fasting glucose (mmol/L); TC – total cholesterol (mmol/L); HDL&LDL – high- and low-density lipoprotein cholesterol (mmol/L); TG – triglycerides (mmol/L); CHD – coronary heart disease [Y/N]; CI – cerebral infarction [Y/N]; DM – diabetes mellitus [Y/N]; HAMD17 – total scores of 17-item Hamilton Rating Scale for Depression.

Endothelial dysfunction is a critical step in the development of cardiovascular disease, such as hypertension, atherosclerosis, and thrombosis [29]. Several studies have demonstrated that endothelial function has relevance to blood pressure and lipids, which are cardiovascular risk factors. The relationship between depression symptoms and endothelial function is complicated. Some cross-sectional studies and retrospective studies [14,30–32] showed that depression in adolescence [14,20], climactereium [32,33] and senility, unipolar depression, bipolar depression [15], major depressive episodes, and minor depressive symptoms [6,20] were closely associated with endothelial dysfunction. Regarding biological mechanisms, depression may reduce synthesis of nitric oxide synthase [34] and create imbalance between dilation (by NO) and contraction (by ET-1) of blood vessels, which finally causes endothelial dysfunction. Depression directly influences the HPA axis and causes its overactivity to increase cortisol levels [35,36]. Cortisol may impair endothelial function. According to the behavioral mechanisms, depression may cause obesity [20], reduced exercises, and disturbed metabolism of glucose and lipid, which indirectly result in endothelial dysfunction. However, several studies [16,37] found a relationship between depression and CHD [16] and DM [37,38]. In the present study, patients were recruited from a general hospital in China, and results showed that DBP, TG, CHD, and HAMD total scores had significant effects on RHI, consistent with previous research [16].

Another important result in the present study was that the improvement of depression was accompanied by improvement of endothelial function. This may be ascribed to the following reasons: 1) endothelial dysfunction is dependent on depressive status. The improvement of depression may cause the cortisol

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Table 2. Clinical variables showed association with RHI in univariate analysis.

Variables	Parameter estimates	Standard error	t value	P value
Gender	0.03924	0.08771	0.45	0.6551
Age	–0.00407	0.00449	–0.91	0.3656
BMI	–0.01882	0.0152	–1.24	0.2172
SBP	–0.0055	0.00402	–1.37	0.1727
DBP	–0.01099	0.0047	–2.34	0.0205
FG	–0.02967	0.0214	–1.39	0.1672
TC	0.0005933	0.04556	0.01	0.9896
HDL	–0.10653	0.0994	–1.07	0.2852
LDL	0.07075	0.06099	1.16	0.2475
TG	–0.09247	0.04508	–2.05	0.0417
CHD	–0.4097	0.09083	–4.51	<0.0001
CI	–0.0038	0.09739	–0.04	0.9692
DM	0.03883	0.11379	0.34	0.7333
HAMD17	–0.0153	0.00268	–5.72	<0.0001

BMI – body mass index (kg/m^2); SBP – systolic blood pressure (mmHg); DBP – diastolic blood pressure (mmHg); FG – fasting glucose (mmol/L); TC – total cholesterol (mmol/L); HDL&LDL – high- and low-density lipoprotein cholesterol (mmol/L); TG – triglycerides (mmol/L); CHD – coronary heart disease [Y/N]; CI – cerebral infarction [Y/N]; DM – diabetes mellitus [Y/N]; HAMD17 – total scores of 17-item Hamilton Rating Scale for Depression.

secretion to become normal in the HPA axis. In the presence of stress, metyrapone, a drug able to inhibit the secretion of cortisol, is able to prevent endothelial dysfunction [36]. In our study, the endothelial function was measured on the basis of NO and was mainly characterized by vascular dilation. After anti-depressant therapy, the β receptor might become normal, leading to vascular dilation [15]. 2) Antidepressants may improve the endothelial function. Pizzi et al. [39,40] found the improvement of depression in CHD patients with depression following anti-depressant therapy was accompanied by the improvement of endothelial function. There is evidence showing that the endothelial dysfunction is still present in depression patients after anti-depressant therapy [13,15]. Among clinical studies, only the SADHART study [41] indicated that SSRIs might reduce the morbidity and mortality related to cardiovascular and cerebrovascular diseases. The evidence is still not enough to establish that successful anti-depressants therapy can reduce the incidence of cardiovascular events and/or increase the survival rate of these patients. Although the effect of SSRIs on nitric oxide synthase and NO production is ambiguous [40], anti-depressants as a confounding factor might obscure the relationship with endothelial function. In the present study, the influence of anti-depressants therapy on this relationship was excluded and results confirmed that the endothelial function recovered 3 months after discontinuation of anti-depressants therapy when clinical remission of depression was confirmed, and the endothelial function in

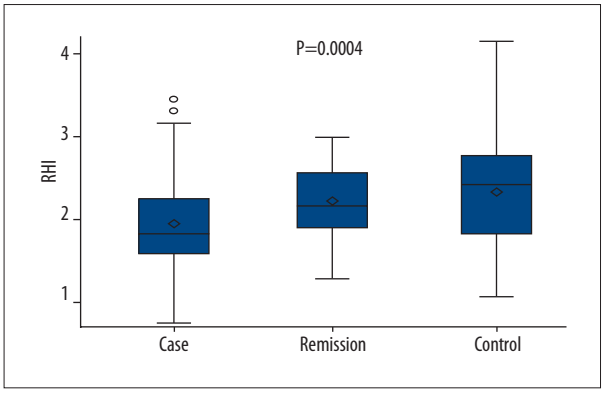

Figure 1. RHI of patients in the 3 groups.

remission patients was comparable to that of non-depression patients. Our findings are consistent with previously reported research [16] and demonstrate that the endothelial function after anti-depressants treatment could recover to the level of healthy controls.

EndoPAT2000 is able to identify atherosclerosis at an early stage and predict the adverse cardiovascular outcomes within 7 years [11]. This study for the first time employed EndoPAT for the non-invasive quantitative evaluation of vascular endothelial function in outpatients recruited from a general hospital. Our findings are consistent with results obtained with other methods for the detection of endothelial function. Thus, this

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technique is applicable in clinical studies on general screening and our results may be generalized.

This was a cross-sectional study that failed to evaluate the causative relationship between depression and endothelial function. This causative relationship needs to be confirmed in future prospective studies with larger sample sizes. Although paired comparisons were done among the 3 groups after balancing the clinical characteristics of subjects in these groups, which is a novelty of this study, the course of depression and details of anti-depressants therapy were not analyzed and evaluated. In future studies, investigators may focus on the relationship of changes in depression status with changes in endothelial function of a specific individual.

Conclusions

Taken together, depression in outpatients from a general hospital in China is closely related to endothelial dysfunction. The improvement of depression after anti-depression therapy is accompanied by improvement of endothelial function, which returns to a level comparable to that in healthy controls. Further studies with larger sample sizes are required to confirm these results.

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