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Plasma levels of lipoprotein (a) in patients with major depressive disorders

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ABSTRACT

Depression and cardiovascular disease are among the most prevalent health problems. The evidence that depression is a risk factor for the development and progression of coronary heart disease has strengthened over the past several years, but the exact reasons are not yet clear. Elevated lipoprotein (a) (Lp(a)) concentrations seem to be the major factor for the progression of the atherosclerosis and coronary heart disease. In this study, we measured the plasma levels of Lp(a) in 35 patients with major depressive disorder and 35 healthy controls. The two groups were matched by age and gender. Lp(a) measurement was performed using an immunoturbidimetric method. Total cholesterol was significantly lower in the patient group (mean ± SD: 144.65 ± 22.13 vs. 186.14 ± 34.48 mg/dl. The Lp(a) levels of the patient group differed significantly from control values. Patients with major depressive disorder had higher plasma levels of Lp(a) than healthy controls (34.94 ± 18.01 vs. 20.08 ± 11.27 mg/dl). The results of the present study suggest that the increase of Lp(a) may contribute to higher cardiovascular risk in patients with major depressive disorder.

1. Introduction

Major depressive disorder and cardiovascular diseases are the two leading causes of worldwide disability (Murray and Lopez, 1997). They are among the top five chronic disorders encountered in the care of older patients (Sherbourne et al., 1997; Terres et al., 1995; Whooley, 2006). Patients with depression have a two- to four-fold increased risk of developing cardiovascular disease and mortality after experiencing cardiac events (Ariyo et al., 2000; Joynt et al., 2003; Lesperance et al., 2002). Because of expected changes in worldwide demographics, it is predicted that by 2020, coronary heart disease and depression will account for the greatest proportion of the global burden of disease (Nancy and Lespérance, 2005).

The relation between depression and coronary heart disease has been the subject of research for more than 30 years, and over that time, the evidence of links between them has continued to grow (Frasure-Smith and Lespérance, 2006). Although many biological and behavioral mechanisms have been proposed to explain the link between coronary heart disease and depression, their relative importance remains unknown (Joynt et al., 2003). Alterations in cardiac autonomic tone (Carney et al., 2001), common genetic vulnerability (McCaffery et al., 2006), enhanced activity of the hypothalamic-pituitary-adrenal axis (Otte et al., 2004), greater platelet activation (Serebruany et al., 2003), increased catecholamine levels (Otte et al., 2005), increased whole blood serotonin (Schins et al., 2004), inflammatory processes (Empana et al., 2005), lower omega-3 fatty acid levels (Frasure-Smith et al., 2004), mental-stress induced ischemia (Strike and Steptoe, 2003), toxicity of tricyclic antidepressants (Cohen et al., 2000), dietary factors (Ziegelstein et al., 2000), lack of exercise (Ruo et al., 2004), medication nonadherence (Gehi et al., 2005), poor social support (Barefoot et al., 2003), and unhealthy lifestyle (Bonnet et al., 2005) could at least in part account for this association.

Since Berg identified lipoprotein (a) in human plasma in the early sixties (Berg, 1963), there has been ongoing research on the nature and metabolism of Lp(a) and its role in atherogenesis. Lp(a) is a very heterogeneous particle and its lipid moiety is similar to the low density lipoprotein, including its cholesterol ester-rich core. Each Lp (a) particle possesses apolipoprotein (a) that is linked to apolipoprotein B100 by a single disulfide bond (Marcovina et al., 2003).

Increased serum lipoprotein (a) levels have been associated with atherothrombotic disease in several studies (Craig et al., 1998; Danesh et al., 2000; Enas and Senthilkumar, 2002; Gambhir et al., 2000; Geethanjali et al., 2002; Gupta et al., 1996; Keller, 2007; Luc et al., 2002; Mohan et al., 1998; Nguyen et al., 1997).

Lp(a) excess increases the risk of premature coronary heart disease about 3- to 100-fold depending on the absence or presence of concomitant risk factors (Hopkins et al., 1997). In previous reports, a plasma Lp(a) level higher than 25 mg/dl was an independent risk factor for atherosclerosis with coronary manifestations (Emanuele et al., 2006; Miwa et al., 2000; Rajasekhar et al., 2004; Terres et al., 1995).

Coronary heart diseases are common among major depressive patients (Bonnet et al., 2005; Morrisett, 2000; Rajasekhar et al., 2004; Schins et al., 2004) but the exact causes are not clear. Levels of Lp(a) in patients with major depression have been reported (Emanuele et al.,

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2006; Sarandol et al., 2006), and our study was undertaken to explore why such patients are at heightened cardiovascular risk: Does Lp(a) play a role in this association?

2. Methods

2.1. Subjects

The study had a case-control, -cros sectional designs. The sample comprised 70 subjects in two groups (35 major depression patients and 35 normal controls). The sample size was chosen according to data from Emanuele et al. (Emanuele et al., 2006), with power (β) of 80% and $\alpha = 0.05$. All major depressive patients had been admitted to a medical institution for treatment (Asadabadi Hospital in Tabriz City), and all were assessed in an in-patient setting. They had major depressive disorder according to DSM-IV. All patients were assessed with the Beck Depression Inventory (BDI) and a psychiatric interview with a psychiatrist.

Cases were aged between 18 and 65 years. Exclusion criteria were: age <18 or >65 years; a positive history of atherothrombotic events (coronary heart disease, stroke, peripheral artery disease, venous thromboembolism); history of cholesterol-lowering treatment; the presence of any endocrinological problem or physical illness; and the presence of abnormality on hematological, renal and liver function tests. Psychiatric exclusion criteria were: eating disorders, anxiety disorders and mental retardation, the history of alcohol and substance dependence or use, and treatment with psychiatric medication within the last 6 months. Subjects with co-morbid psychiatric disorders were also excluded.

The normal control group consisted of 35 healthy subjects recruited from staff, students and volunteers at our institution. Controls had no current or past psychiatric illnesses that had been diagnosed by a psychiatrist. The controls, like the patients, were assessed with the Beck Depression Inventory. They were matched with the cases by gender and age. Exclusionary criteria were the same as those for the patients.

The study design was approved by the university ethical committee. After a complete description of the study, all patients and healthy controls gave informed consent to participate in the investigation.

2.2. Biochemical measurements

After an overnight fast, venous blood samples were drawn from the antecubital vein at 08:00 a.m. and the separated plasma was stored at −70 °C until analyzed. WBC, RBC, HG, HCT, MCV, MCH, and MCHC were determined using standard methods (cell counter model cell taca machine, Japan). Serum creatinine, as an index of renal function, was assessed by Pars Azmun kite (Iran). Plasma glucose, total cholesterol, HDL-cholesterol and triglycerides were measured using enzymatic and colorimetric procedures by Pars Azmun kite (Iran) with Autoanalysor (Alcyon 300). LDL-cholesterol concentrations were calculated according to Friedewald's Formula (Friedewald et al., 1972), as: LDL-cholesterol = Total cholesterol − (HDL-cholesterol + Triglyceide/5). Body Mass Index (BMI = weight (kg)/height^2 (m)) was calculated as an indicator of nutritional status.

Plasma Lp(a) measurement was performed using an immunoturbidimetric method by Randox kite (United Kingdom) with Autoanalysor (Alcyon 300). This technique is an endpoint determination of the concentration of Lp(a) through photometric measurement of antigen–antibody reaction between antibodies to Lp(a) and Lp(a) present in the sample (Molinari et al., 1995).

Table 1
Characteristics and plasma lipoprotein (a) levels of the study groups.

	Major depression ($n = 35$)	Healthy controls ($n = 35$)	P value
Age(years)	35.2 ± 10.72	33.71 ± 10.21	0.55
Sex			
Male (%)	17.1	17.1	
Female (%)	82.9	82.9	
Body mass index (kg/m^2)	25.82 ± 4.41	24.77 ± 7.2179	0.95
White blood cells (10^3 per μl)	6.05 ± 1.62	5.72 ± 1.22	0.35
Red blood cells (10^6 per μl)	5.01 ± 0.49	4.82 ± 0.39	0.08
Hemoglobin (g/dl)	13.81 ± 1.27	14.05 ± 1.08	0.40
Hematocrit (%)	40.38 ± 3.87	41.72 ± 2.65	0.09
Mean cell volume (fl)	82.54 ± 6.16	84.90 ± 6.05	0.11
Mean cell hemoglobin (pg)	28.34 ± 3.16	29.69 ± 2.81	0.06
Mean cell hemoglobin concentration (g/dl)	32.99 ± 1.29	33.20 ± 1.97	0.59
Plasma glucose (mg/dl)	92.34 ± 6.52	88.91 ± 14.71	0.21
Creatinine (mg/dl)	0.80 ± 0.11	0.85 ± 0.10	0.10
Total cholesterol (mg/dl)	144.65 ± 22.13	186.14 ± 34.48	0.0001
Triglycerides (mg/dl)	120.8 ± 25.40	120.08 ± 19.28	0.97
HDL-cholesterol (mg/dl)	47.71 ± 9.45	51.91 ± 13.99	0.14
LDL-cholesterol (mg/dl)	72.78 ± 17.75	110.21 ± 31.23	0.0001
Lipoprotein (a) (mg/dl)	34.94 ± 18.01	20.08 ± 11.27	0.0001
Beck depression inventory score	32.02 ± 2.95	7.17 ± 1.56	0.0001

Data are expressed as mean ± standard deviation.

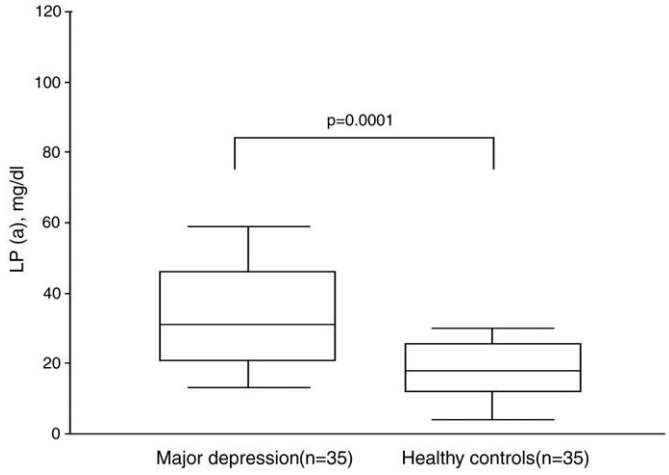

Fig. 1. Box plots with plasma lipoprotein (a) levels in the study groups referring to differences between the major depression group and controls.

2.3. Statistical analysis

All statistical analyses were performed with the SPSS 11.5 software. Normally distributed data are presented as mean ± S.D. Student's t-test (independent sample t-test) was performed for comparisons between two groups. The Chi-Square test was used to analyze the categorical data. Pearson's coefficient of correlation was calculated to assess possible links between Lp(a) concentrations, BDI scores and clinicolaboratory aspects of the subjects. The level of significance was set to $P < 0.05$.

3. Results

The results obtained are summarized in Table 1. The two groups were well matched with regard to age and gender. There were no significant differences among the groups for mean age and female/male ratio.

No differences in hematological parameters were detected between groups. In addition, there were no significant differences among the groups in levels of serum creatinine, plasma glucose, HDL-cholesterol and triglycerides. Body mass index was not different between groups. Total cholesterol and LDL-cholesterol levels showed significant differences among groups ($P = 0.0001$).

Plasma Lp(a) concentrations are presented in Fig. 1. Lp(a) levels were significantly different ($P = 0.0001$) between the two groups. Lp

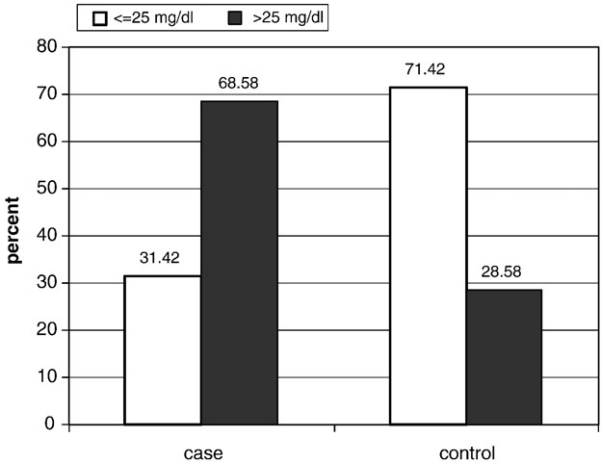

Fig. 2. Percentages of subjects with lipoprotein (a) below or above 25 mg/dl in the two groups.