

## CLINICAL SCIENCE

# Relationship between depression and apolipoproteins A and B: a case-control study

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**OBJECTIVE:** To investigate the relation between major depressive disorder and metabolic risk factors of coronary heart disease.

**INTRODUCTION:** Little evidence is available indicating a relationship between major depressive disorder and metabolic risk factors of coronary heart disease such as lipoprotein and apolipoprotein.

**METHODS:** This case-control study included 153 patients with major depressive disorder who fulfilled the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), and 147 healthy individuals. All participants completed a demographic questionnaire and Hamilton rating scale for depression. Anthropometric characteristics were recorded. Blood samples were taken and total cholesterol, high- and low-density lipoproteins and apolipoproteins A and B were measured. To analyze the data, t-test,  $\chi^2$  test, Pearson correlation test and linear regression were applied.

**RESULTS:** Depression was a negative predictor of apolipoprotein A ( $\beta = -0.328$ ,  $p < 0.01$ ) and positive predictor of apolipoprotein B ( $\beta = 0.290$ ,  $p < 0.05$ ). Apolipoprotein A was inversely predicted by total cholesterol ( $\beta = -0.269$ ,  $p < 0.05$ ) and positively predicted by high-density lipoprotein ( $\beta = 0.401$ ,  $p < 0.01$ ). Also, low-density lipoprotein was a predictor of apolipoprotein B ( $\beta = 0.340$ ,  $p < 0.01$ ). The severity of depression was correlated with the increment in serum apolipoprotein B levels and the decrement in serum apolipoprotein A level.

**CONCLUSION:** In view of the relationship between apolipoproteins A and B and depression, it would seem that screening of these metabolic risk factors besides psychological interventions is necessary in depressed patients.

**KEYWORDS:** Coronary risk factors; Coronary heart disease; Major depression.

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## INTRODUCTION

Major depressive disorder (MDD) is the most common mood disorder with a significant effect on the progression of medical conditions.<sup>1</sup> Factors accompanying depression, such as patients' failure to look after their health, inability to adapt to their environment, social dissociation, chronic stresses of life, cigarette smoking, reduced physical activity, inappropriate nutrition and poor compliance with medical advice, make depression one of the risk factors of non-communicable diseases.<sup>2</sup>

In addition to the effect of depression on lifestyle, the direct effect of depression on metabolic factors has been shown in many studies.<sup>3</sup> Recently, a relationship has been observed between depression and serum levels of lipoproteins and apolipoproteins (apo), which are known risk factors of obesity and cardiovascular diseases.<sup>4</sup> One theory of this relationship suggests a disturbance in function of the serotonergic system. In addition, metabolic changes in patients with MDD are due to genetic changes in the coding of serum lipoproteins.<sup>5</sup> Other theories describe changes in interleukin 2, number of total T-cells, melatonin and other cytokines in depressed patients.<sup>6-8</sup>

Despite these studies, controversy exists about the relationship between depression and the lipid profile. Studies have shown different results for the level of apo A—one of the high-density lipoprotein cholesterol (HDL-C) subgroups, and of apo B—the major protein of low-density lipoprotein cholesterol (LDL-C), in patients with MDD.<sup>4,9,10</sup>

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Sevincok and Sarandol showed that the serum level of apo A in depressed patients was lower than that in control group.<sup>4,9</sup> Another study showed no significant difference in the serum levels of apolipoproteins between depressed patients and the control group.<sup>11</sup>

The lack of evidence and controversial results of previous studies led us design this study to compare the serum levels of apolipoproteins in depressed patients and normal individuals.

## METHODS

A population of 153 patients with MDD (63 women, 90 men, aged 21–47 years) in 2007 were included in this case-control study. All the patients were diagnosed with MDD according to the Structured Clinical Interview (SCID-I) for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Relatives of hospitalized patients and hospital university staff comprised the control group (78 women, 69 men, aged 18–47 years).

### Exclusion Criteria

Patients with an axis I or II disorder in addition to their depression, patients with MDD with psychotic features, bipolar disorder, cyclothymia, dysthymia, anxiety disorder and patients at significant risk of suicide were excluded from the study via the structured clinical interview for DSM-IV.

Exclusion criteria for both case and control groups included the presence of organic diseases such as hypertension, diabetes, cardiovascular, adrenal, hepatic and thyroid diseases documented by physical examination and laboratory tests; history of anti-lipid and  $\beta$ -blocker consumption; and menopause in women.

Laboratory tests, including complete blood count, serum electrolyte assay, liver function tests, thyroid function tests, urine analyses and electrocardiography, were performed for all participants to screen for major health problems. In addition, after explanation of the study, informed consent was obtained from all participants. The study protocol was approved by the ethical committee of the Isfahan University of Medical Sciences.

### Measurements

All participants completed a self-administered questionnaire to determine demographic characteristics such as age, gender, socioeconomic status (occupation, marital status and educational level), smoking status, drug history, family history of depression, physical activity and diet. Subjects were considered to be "current smokers" if they reported smoking at least one cigarette a day during the past year.

Anthropometric characteristics (height and weight) were measured with the subjects wearing thin clothes. Body mass index (BMI) was calculated by dividing a participant's weight by their height squared ( $\text{kg}/\text{m}^2$ ). Regular physical activity was defined as exercise of at least 15 minutes' duration at least twice each week.<sup>13</sup>

Participants provided details of their dietary habits by completing a Food Frequency Questionnaire (FFQ).<sup>14</sup> This instrument was designed according to the WHO-FFQ, with some changes. The validity of this questionnaire was confirmed before its use by the Medical Education Development Center affiliated to Isfahan University of Medical Sciences.<sup>15</sup> The FFQ was used to access the

consumption of different food groups such as meat, oils, cereals, vegetables and fruits.

Eligible participants also completed a 17-item Hamilton rating scale for Depression (HAM-D), which is the most commonly used observer-rated depressive symptom rating scale. The original scale has 21 items but, as Hamilton has suggested, only the initial 17 items were scored in this study because the last 4 items rarely occur and deal only with aspects of illness. Items with quantifiable severity were ranked on a scale of 0–4 and those measuring symptoms that are difficult to assess reliably were ranked on a scale of 0–2. The range of the 17-item scale was 0–50, with 14 considered to be the cut-off point of this scale; higher scores indicated more severe depression. According to HAM-D, patients were classified into 3 groups of mild MDD (score 15–18), moderate MDD (score 19–22) and severe MDD (score  $\geq 23$ ).<sup>16,17</sup>

A blood sample was taken after 12–14 hours' fasting through the antecubital vein. All the blood sampling procedures were performed in the central laboratory of the Isfahan Cardiovascular Research Centre. Serum triglyceride (TG), total cholesterol (TC), HDL-C, LDL-C and apo A and B were measured for each patient. TC and TG levels were measured within 24 h by an enzymatic method using an Elan 2000 autoanalyze. HDL-C was assayed by the direct method. LDL-C was calculated by the Friedewald formula,<sup>18</sup> but in cases with  $\text{TG} \geq 400 \text{ mg}/\text{dl}$ , it was measured directly. Apo A and B were measured by immunoturbidimetry using Pars Azmoon kits accredited by Bioactiva Diagnostica (Germany).

### Statistical Analysis

Continuous variables were expressed as mean  $\pm$  SD and a *t*-test was used to compare the means between the two groups. Qualitative variables were expressed as frequency and a  $\chi^2$  test used to compare frequencies between the two groups.

A Pearson correlation test was used to evaluate the correlation of depression with apo A and apo B. To study the association of depression and apo A and B (apo A and B, separately), multiple linear regression models were used. Apo A and B were entered as dependent variables, and the group (case vs. control), smoking status (smokers vs. non-smokers), BMI, TC, LDL-C and HDL-C were entered as independent variables. The enter approach was selected for regression model, and for each apo A and B a unique model was created. The presumption of a linear regression model was used for both models.

Data were analyzed by SPSS version 15.0 (SPSS Inc, Chicago, Illinois, USA). A *p*-value  $< 0.05$  was considered significant.

## RESULTS

Table 1 showed the baseline characteristics of participants. The baseline variables sex, age, marital state and occupation were similar in case and control groups. The mean age of participants was  $31.21 \pm 10.41$  years in the group with MDD vs.  $32.00 \pm 8.21$  years in the control group. Depressed patients were significantly more likely to have a family history of depression and a past history of smoking ( $p < 0.05$ ).

The duration of depression was  $4.07 \pm 1.84$  years in patients. Fifty-four patients were mildly depressed (35.3%), 69 were moderately depressed (45.1%) and 30 were severely

**Table 1 - Basic characteristics of case (n = 153) and control (n = 147) groups.**

Characteristics	MDD group (N= 153)		Control group (N= 147)		p-Value <sup>†</sup>
	Mean ± SD		Mean ± SD		
Age (years)	31.21 ± 10.41		32.00 ± 8.21		NS*
Body mass index (kg/m <sup>2</sup> )	22.06 ± 3.23		21.50 ± 3.01		NS
Cholesterol (mg/dl)	158.03 ± 27.69		136.59 ± 28.59		0.06
Low-density lipoprotein (mg/dl)	92.96 ± 20.74		79.59 ± 21.31		0.01
High-density lipoprotein (mg/dl)	35.96 ± 7.39		44.65 ± 8.26		0.03
Apolipoprotein A (mg/dl)	130.78 ± 24.44		151.09 ± 34.20		≤0.001
Apolipoprotein B (mg/dl)	91.78 ± 26.54		85.71 ± 25.82		0.05
Hamilton Depression Rating Scale	20.8 ± 10.07		3.96 ± 1.73		≤0.001
	N	%	N	%	p-Value <sup>‡</sup>
Sex					NS
Men	90	58.8	69	46.9	
Women	63	41.2	78	53.1	
Occupation					NS
Unemployed	54	35.3	51	34.7	
Home worker	33	21.6	39	26.5	
Salary employed	42	27.5	42	28.6	
Self-employed	24	15.7	15	10.2	
Marital status					NS
Married	87	56.9	90	61.2	
Unmarried(single, widow, divorced)	66	43.1	57	38.8	
Educational level					NS
0-5 years	54	35.3	51	34.7	
6-12 years	45	29.4	39	26.5	
>12 years	54	35.3	57	38.8	
Positive family history					0.04
Yes	30	19.6	6	4.1	
No	123				
Smoking					0.02
Yes	60	39.3	24	16.3	
No	93	60.7	123	83.7	

\*NS, not significant.

<sup>†</sup>p-Values were based on t-test.

<sup>‡</sup>p-Values were based on  $\chi^2$  test.

depressed (19.6%). There were no statistically significant differences between the two groups in BMI and physical activity. Consumption of different groups of foods, which was assessed by the FFQ, showed no significant statistical difference between the two groups.

Concentrations of all serum lipids and apo A and B differed significantly between the two groups. TC, LDL-C and apo B were higher, while HDL-C and apo A were lower, in the case group than in controls (Table 1).

Linear regression analysis showed that serum apo A levels were negatively ( $p < 0.01$ ) and serum apo B levels were positively ( $p < 0.05$ ) predicted by depression. Serum TC levels predicted negatively ( $p < 0.05$ ) and HDL-C levels predicted positively ( $p < 0.01$ ) the serum apo A levels.

LDL-C levels predicted positively the serum apo B levels ( $p < 0.01$ ). Smoking status and BMI did not significantly predict the apo A and B levels (Table 2).

The correlation between depression severity according to HAM-D and serum levels of the apolipoproteins indicated an inverse relationship between depression severity and serum apo A levels ( $r = -0.453$ ,  $p < 0.01$ ) and a direct relationship between depression severity and serum apo B levels ( $r = 0.521$ ,  $p < 0.05$ ).

## DISCUSSION

Our findings showed a significant correlation between serum levels of apolipoproteins and depression so that the

**Table 2 - Predictors of serum apolipoprotein A and apolipoprotein B levels.**

Variables	Apolipoprotein A		Apolipoprotein B	
	Standardized $\beta$	p-Value	Standardized $\beta$	p-Value
Group*	-0.328	0.008	0.290	0.022
Smoking status <sup>†</sup>	0.137	0.248	-0.099	0.479
Body mass index (kg/m <sup>2</sup> )	0.074	0.543	0.101	0.453
Total cholesterol (mg/dl)	-0.269	0.044	0.066	0.687
Low-density lipoprotein (mg/dl)	0.159	0.094	0.340	0.006
High-density lipoprotein (mg/dl)	0.401	0.001	-0.024	0.854
Adjusted R <sup>2</sup>	0.227		0.200	

\*Depressed patient = 1; control = 0.

<sup>†</sup>Smoker = 1; non-smoker = 0.

serum level of HDL-C and apo A were lower, while LDL-C and apo B (atherogenic lipoproteins) were higher, in patients with MDD than those in the control group. In addition, severity of depression correlated with an increment in serum apo B level and a decrement in serum apo A level.

Only a few studies have investigated the serum apolipoprotein levels in patients with MDD. Sarandol et al. investigated the oxidation of apo B-containing lipoproteins and the serum paraoxonase and arylesterase activities in MDD. Their case group included patients with MDD who had not received antidepressant drugs for at least 3 weeks. Higher TC, HDL-C, LDL-C and apo B, and lower apo A, levels were found in the case group. The patients were treated with a standard dosage of antidepressant drugs for 6 weeks, which did not alter the serum levels of lipid profiles.<sup>4</sup> However, there is some evidence that antidepressant agents may affect serum lipid profile levels.<sup>9</sup> Thus, we excluded patients who had taken antidepressant drugs during the past 6 months. Our results, except those for HDL-C, were in line with those of Sarandol et al.

Association between serum HDL-C and LDL-C levels as predictors of coronary heart disease (CHD) and MDD is one of the fields which has been investigated.<sup>19</sup> Few studies have shown an inverse association between them.<sup>2</sup> A meta-analysis on the association of cholesterol and depression showed that TC and depression were inversely related.<sup>21</sup> On the other hand, some studies, such as that of Chen et al., demonstrated lower HDL-C and higher LDL-C and TC levels in patients with MDD.<sup>22</sup> Similarly, Nakao and Yano showed significant direct association between hypercholesterolemia and patients with MDD in Japanese men.<sup>23</sup> Since apo A is known to be a major fraction of HDL-C and apo B is known to be a major fraction of LDL-C, our results were in accordance with the results of these studies.

Depression is associated with CHD—that is, depressed patients are more prone to develop CHD.<sup>24,25</sup> Because of this association, the relationship between depression and other risk factors of CHD such as serum apolipoprotein levels is an important subject that should be examined more closely. There are some biological hypotheses which may explain this association. One hypothesis suggests that genetic factors associated with depression may contribute to a change in serum lipid levels.<sup>26</sup> A second theory proposes that cholesterol may be an important factor in reducing the possibility of correction of metabolic defects. As a result of these defects, segmental cerebral hypoxia, which may be associated with depression, could occur.<sup>27</sup> Altered lipid profile levels through changes in serotonergic systems might also lead to MDD.<sup>28</sup>

This study has some limitations. Owing to the cross-sectional design of the study, the cause and effect relationship and mechanisms of the association between depression and lipid profile could not be determined. Also, some of our data were based on self-reported questionnaires, which are less reliable sources of information than direct measurement. Also, as previously mentioned, although our case and control groups had no differences in socioeconomic status, some of the control group comprised university hospital staff.

## CONCLUSION

The results of the study demonstrated lower serum levels of apo A and HDL-C and higher serum levels of apo B and

LDL-C in depressed patients than in the control group. Thus in depressed patients, biochemical problems should be considered and evaluated together with psychological interventions. Given the relationship between apolipoproteins and depression, checking the lipid profile as predicting factors of CHD to prevent the appearance of extra cardiovascular risk factors seems necessary.

## REFERENCES

1. Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KR, et al. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry*. 2005;58:175-89, doi: 10.1016/j.biopsych.2005.05.001.
2. Schulz R, Beach SR, Ives DG, Martire LM, Ariyo AA, Kop WJ. Association between depression and mortality in older adults: the cardiovascular Health study. *Arch Intern Med*. 2001;160:1761-8, doi: 10.1001/archinte.160.12.1761.
3. Huang TL, Chen JF. Lipid and lipoprotein levels in depressive disorders with melancholic feature or atypical feature and dysthymia. *Psychiatry Clin Neurosci*. 2004;58:295-9, doi: 10.1111/j.1440-1819.2004.01235.x.
4. Sarandol A, Sarandol E, Eker S, Hizli B, Kirli S, Dirican M, et al. Oxidation of apolipoprotein B-containing lipoproteins and serum paraoxonase/arylesterase activities in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30:1103-80, doi: 10.1016/j.pnpbp.2006.04.012.
5. Partonen T, Haukka J, Virtamo J, Taylor PR, Lonnqvist J. Association of low serum total cholesterol with major depression and suicide. *Br J Psychiatry*. 1999;175:259-62, doi: 10.1192/bjp.175.3.259.
6. Buckley TM, Schatzberg AF. A pilot study of the phase angle between cortisol and melatonin in major depression - a potential biomarker. *J Psychiatr Res*. 2010;44:69-74, doi: 10.1016/j.jpsychires.2009.06.012.
7. Kabanchik A, Toll G, Segall D, Arienza J, Dobrenky de Rudoy S. Importance of interleukin 2 soluble receptors determination in patients over 60 years with untreated depression. *Vertex*. 2004;15:41-4.
8. Mohr DC, Genain C. Social support as a buffer in the relationship between treatment for depression and T-cell production of interferon gamma in patients with multiple sclerosis. *J Psychosom Res*. 2004;57:155-8, doi: 10.1016/S0022-3999(03)00601-9.
9. Kopf D, Westphal S, Luley C, Ritter S, Gilles M, Heuser I, et al. Lipid metabolism and insulin resistance in depressed patients. *J Psychopharmacology*. 2004; 24:527-31, doi: 10.1097/01.jcp.0000138762.23482.63.
10. Sevincok L, Buyukozturk A, Dereboy F. Serum concentrations in patients with comorbid anxiety disorder and major depressive disorder. *Can J Psychiatry*. 2006;46:68-71.
11. Severus WE, Littman AB, Stolln AL. Omega-3 fatty acids, homocysteine and the increased risk of cardiovascular mortality in major depressive disorder. *Harv Rev Psychiatry*. 2001;9:280-93, doi: 10.1080/10673220127910.
12. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, fourth ed. text revision. Washington, DC: American Psychiatric Association. 2000.
13. Andersen RE, Wadden TA, Bartlett SJ, Zemel B, Verde TJ, Franckowiak SC. Effects of lifestyle activity vs structured aerobic exercise in obese women: a randomized trial. *JAMA*. 1999;281:335-40, doi: 10.1001/jama.281.4.335.
14. Dwyer TT. Dietary assessment. In: Shils ME, Olson JA, Shike M, editors. *Modern Nutrition in Health and Disease*. 8th ed. Philadelphia: Awaverly Co; 1994. p. 842.
15. Sarraf-Zadegan N, Sadry G, Malek Afzali H, Baghaei M, Mohammadi Fard N, Shahrokhy S, et al. A comprehensive integrated community-based program for cardiovascular disease prevention and control. *Acta Cardiologica*. 2003;58:309-20, doi: 10.2143/AC.58.4.2005288.
16. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62, doi: 10.1136/jnnp.23.1.56.
17. Shabani A, Akbari M, Dadashi M. Reliability and validity of the bipolar depression rating scale on an Iranian sample. *Arch Iran Med*. 2010;13:218-22.
18. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499-502.
19. Hemingway H, Marmot M. Evidence based cardiology: psychosocial factors in the etiology and prognosis of coronary artery disease. *BMJ*. 1999;318:1460-7.
20. Suarez EC. Relations of trait depression and anxiety to low lipid and lipoprotein concentrations in healthy young adult women. *Psychosomatic Med*. 1999;61:273-9.
21. Shin JY, Suls J, Martin R. Are cholesterol and depression inversely related? A meta-analysis of the association between two cardiac risk factors. *Ann Behav Med*. 2008;36:33-43, doi: 10.1007/s12160-008-9045-8.

22. Chen CC, Lu FH, Wu JS, Chang CJ. Correlation between serum lipid concentrations and psychological distress. *Psychiatry Res.* 2001;102:153-62, doi: 10.1016/S0165-1781(01)00231-1.
23. Nakao M, Yano E. Relationship between major depression and high serum cholesterol in Japanese men. *Tonoku J Exp Med.* 2004;204:273-87, doi: 10.1620/tjem.204.273.
24. Strike P, Steptoe A. Depression, stress and the heart. *Heart.* 2002;88:441-3, doi: 10.1136/heart.88.5.441.
25. Rugulies R. Depression as a predictor for coronary heart disease. A review and meta-analysis. *Am J Prev Med.* 2002;23:51-61, doi: 10.1016/S0749-3797(02)00439-7.
26. Sobczak S, Honig A, Christophe A, Maes M, Helsdingen RW, De Vriese SA, et al. Lower high-density lipoprotein cholesterol and increased omega-6 polyunsaturated fatty acids in first-degree relatives of bipolar patients. *Psychol Med.* 2004;34:103-12, doi: 10.1017/S0033291703001090
27. Sepowitz AH, Chien S, Smith FR. Effects of lipoproteins on plasma viscosity. *Atherosclerosis.* 1981;38:89-95, doi: 10.1016/0021-9150(81)90107-6.
28. Terao T, Nakamura J, Yoshimura R, Ohmori O, Takahashi N, Kojima H, et al. Relationship between serum cholesterol levels and meta-chlorophenylpiperazine-induced cortisol responses in healthy men and women. *Psychiatry Res.* 2000;96:167-73, doi: 10.1016/S0165-1781(00)00197-9.