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Lipid levels in female patients with affective disorders

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Abstract

The role of the serum lipids (total cholesterol, high-density lipoprotein cholesterol /HDL-C/, low-density lipoprotein cholesterol /LDL-C/, triglycerides /TG/) in the pathophysiology of the mood disorders is not clear. The aim of this study was to determine lipid profile in patients with affective disorders. The study included medication free female subjects: 41 patients with bipolar disorder (22 in a manic and 19 in a depressive phase), 34 patients with major depression and 50 healthy controls. Serum lipids levels were determined using standard laboratory tests. All patients had significantly lower HDL-C values than control subjects. Increased TG levels were found in patients with bipolar disorder compared to healthy subjects. The changes in lipids profiles persisted when data were adjusted for age, smoking and menopause. The results revealed no differences in the cholestrol and LDL-C levels and body mass index, but significant differences in the ratios of cholesterol/HDL-C and LDL-C/HDL-C values (atherogenic index) among groups. Our results suggest that low HDL-C levels and high atherogenic index might be a hallmark of affective disorders. Since low HDL-C levels could be a risk factor for the development of coronary heart disease, further investigation of the lipids metabolism in affective disorders is warranted.

Key words: Major depressive disorder; Bipolar disorder, mania; Cholesterol, High-density-lipoprotein cholesterol, Low-density-lipoprotein cholesterol, Triglycerides.

1. Introduction

Various studies (Horsten et al., 1997; Maes et al., 1997; Ghaemi et al., 2000; Atmaca et al., 2002; Cassidi and Carroll, 2002; Pae et al., 2004) suggested that pathophysiology of mood disorders might be related to the alterations in the lipid profile. Although in general population women with low levels of high-density lipoprotein cholesterol (HDL-C) (Horsten et al., 1997; Chen et al., 2001) and low cholesterol levels (Horsten et al., 1997) had more depressive symptoms than women with normal lipid levels, the association between total cholesterol, HDL-C, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) levels and affective disorders is still not clear. Namely, clinical studies evaluating the relationship between cholesterol levels and affective disorders yielded inconsistent results. Decreased cholesterol levels were found in patients with mania (Ghaemi et al., 2000; Cassidi and Carroll, 2002; Atmaca et al., 2002; Pae et al., 2004; Sagud et al., 2007), while lower (Maes et al., 1997), or unaltered (Oxenkrug et al., 1983; Huang et al., 2003) serum cholesterol levels were found in female patients with major depression.

A few data presented the entire lipid profile (i.e. cholesterol, HDL-C, LDL-C, TG) in affective disorders. It has been reported that patients with affective disorders had hypocholestrolemia with lower LDL-C and higher HDL-C and TG levels than healthy controls (Glueck et al., 1994), while first degree relatives of bipolar patients had lower HDL-C levels than corresponding healthy controls (Sobczak et al., 2004). Since studies investigating lipid profile in affective disorders, particularly in bipolar disorder in a manic or a depressed phase, are scarce and inconsistent, the aim of the present study was to determine serum levels of total cholesterol, TG, HDL-C and LDL-C in medication-free female patients with major depression and bipolar disorder (in a manic and a depressive episode), and to compare these values with the values in healthy control women.

2. Methods

2.1. Subjects

The study population comprised of 41 female, medication-free inpatients with bipolar I disorders (22 in manic and 19 in depressive episode), 34 female patients with major depression and 50 healthy female subjects. Patients were diagnosed using the structured clinical interview for DSM-IV disorders (APA, 1994). Manic patients scored at least 18 on the Young Mania Rating Scale (YMRS) (Young et al., 1978) and 7 or less on the 17-item Hamilton Depression Rating Scale (HAM-D17) (Hamilton, 1960). Patients with bipolar depression or major depressive disorder scored at least 18 on the HAMD-17, and 5 or less on the YMRS. Exclusion criteria were: a history of schizophrenia, dementia, schizoaffective disorder, alcohol abuse in previous month, serious medical disease (including cardiovascular disease), no change ± 5% of their body weight in the previous 3 months, elevated (>7.0 mmol/L) cholesterol levels, use of cholesterol-lowering drugs, pregnancy, lactation and suicidal behavior (patients who scored 2 or more on item 3 on the HAMD-17). All patients were free of psychotropic medication for at least 2 weeks (washout period ranged between 14 days to 5 years) prior to study entry, except for benzodiazepine equivalent for 2 mg of lorazepam daily. Control group consisted of medication free healthy women, recruited mostly from medical staff, with no personal history of any psychiatric disorder. Nine patients with mania, 7 patients with depressive phase of the bipolar disorder, 13 patients with major depression and 17 healthy controls were in menopause.

Written informed consent was obtained from all participants, under procedures approved by Local Ethics Committee and in accordance with the Helsinki Declaration.

2.2. Blood collection and biochemical measurements

Blood samples were drawn in the morning after an overnight fasting for 12 hours. Serum cholesterol, HDL-C and TG levels were determined by the enzymatic color test for clinical analyzers, with the linearity within concentrations range of 0.64-18 mmol/l, 0.05-4.65 mmol/l and 0.11-11.40 mmol/l for serum cholesterol, HDL-C and TG, respectively. Serum LDL-C levels were determined by enzymatic clearance assay, with linearity up to 22.4 mmol/l.

Body mass index (BMI) was calculated by dividing the weight (in kilograms) by squared height (in meters).

2.3. Statistical procedures

All results were expressed as mean ± S.D. Results were evaluated using one-way analysis of variance (ANOVA), followed by a Tukey's HSD test for multiple comparisons. Analysis of covariance (ANCOVA) was used with age, smoking and menopause as covariates. The significance level was $P<0.05$. The statistical package used was SigmaStat 3.1 and SPSS 11.0.

3. Results

The demographic characteristics of patients and healthy controls are presented in Table 1. No significant difference in age ($F_{3,\ 121}$ =2.011, P=0.11, ANOVA) and BMI ($F_{3,\ 121}$=1.581, P=0.19) was observed between groups.

Serum HDL-C levels were significantly ($F_{3,\ 121}$=22.575, P=0.000) different in healthy controls and patients with major depressive or bipolar disorder (Fig. 1). Significantly lower serum HDL-C values were observed in patients with bipolar disorder in manic (P<0.001; Tukey's HSD) or depressive (P<0.001, Tukey's test) episodes, and with major depression (P<0.001, Tukey's test), when compared to healthy controls. HDL-C levels were significantly different among groups when data were adjusted for age (F_4=18.606, P<0.000), smoking (F_4= 16.838, P<0.000) and menopause (F_4 = 18.968, P<0.000) as covariates (ANCOVA).

There was a significant (F_3 =6.909, P<0.000) difference in serum TG levels among groups (Fig. 2). Patients with bipolar disorders in manic (P=0.007, Tukey's HDS test) or depressive (P<0.001 Tukey's HDS test) episode had significantly higher TG values than healthy controls. Serum TG values were significantly (P<0.048) higher in bipolar disorder in a depressed phase, than in patients with major depression. TG levels were significantly different among groups when data were adjusted for age (F_4 = 5,195, P<0.001), smoking (F_4= 5.787, P<0.000) and menopause (F_4 = 5.139, P<0.001) as covariates (ANCOVA).

Serum cholesterol and LDL-C concentrations did not differ significantly between healthy controls and patients with major depression or bipolar disorder (Table 2). Age (F_4 =1.416, P=0.218; ANCOVA), smoking (F_4 =0.397, P=0.811, ANCOVA) and menopause (F_4 =0.486,

P=0.746, ANCOVA) did not influence serum cholesterol levels among subjects. There was no significant effect of age (F_4 =2.071, *P*=0.089, ANCOVA), smoking (F_4 =1.437, *P*=0.226, ANCOVA) and menopause (F_4 =1.442, *P*=0.224, ANCOVA) on serum LDL-C levels among subjects.

Atherogenic index differed significantly among groups (Table 2). Patients with major depression and patients with both phases of bipolar disorder had significantly (*P*<0.000, Tukey's HSD) higher cholesterol/HDL-C and LDL-C/HDL-C ratios than healthy controls. Patients with bipolar disorder in a depressive phase (Table 2) had significantly (*P*=0.045, Tukey's HSD) higher cholesterol/HDL-C ratio than bipolar patients in a manic phase and patients with major depression (*P*<0.012, Tukey's HSD). The LDL-C/HDL-C ratio was significantly (*P*=0.01, Tukey's HSD) higher in patients with bipolar disorder in a depressive phase than in patients with major depression (Table 2).

4. Discussion

The results of the present study showed that patients with major depression and bipolar disorder (in a manic and a depressed episode) had lower HDL-C values and higher atherogenic index (cholesterol/HDL-C and LDL-C/HDL-C) than control subjects. In addition, we have shown the higher TG levels in patients with bipolar disorder, both in a manic and a depressed phase compared to patients with major depression or healthy controls.

Our data agree with the reported association between low HDL-C levels and depression (Maes et al., 1997; Huang, 2005). Low HDL-C levels were proposed to be a characteristic feature of major depression per se, and not of the subgroups such as melancholia (Maes et al.,

1997, Huang, 2005), treatment resistant depression (Maes et al., 1997), or single or recurrent episodes (Huang, 2005). Our results suggest that lower HDL-C levels and higher atherogenic index, found in patients with major depression, patients with bipolar depression, and patients with mania, might represent a hallmark of affective disorders. These results also agree with the hypothesis that HDL-C might be a trait, rather than a state marker in bipolar disorders (Sobczak et al., 2004).

Lower HDL-C values might be influenced by different factors such as sex, cholesterol-lowering drugs, suicidal behavior, or altered serotonergic function. Sex differences in lipid levels, with lower HDL-C levels (Sudhop, 1999; Zhang et al., 2005) and higher LDL and TG levels (Sudhop, 1999) in healthy men than in healthy women were found. Since present study included only female subjects, lower HDL-C levels were not influenced by sex. Recent suicidal attempts were shown to decrease HDL-C levels in depressed men but not in depressed women (Maes et al., 1997). In our study patients with recent suicidal attempt were not included, and therefore lower HDL-C levels were not due to the history of suicidal behavior. Lower HDL-C levels might result from the altered serotonergic function (Buydens-Branchey et al., 2000), as indicated by the positive correlations between HDL-C levels and serotonin metabolite, 5-hydroxyindoleacetic acid, in suicide attempters (Engstrom et al., 1995), altered platelet serotonin in bipolar disorder (Sagud et al., 2007), and the inverse relationship between platelet serotonin and suicidal behavior in depressed patients (Muck-Seler et al., 1996).

The slight increase in TG values in patients with major depression are in line with higher TG levels found in female patients with major depression, compared to healthy control group (Huang, 2005). It has been suggested that plasma TG concentrations have an important role in

the content and distribution of HDL subclasses (Yang et al., 2005). Mean TG values (>1.69 mmol/L), observed in our patients with bipolar disorders, fit in the values related to higher concentrations of preß$_1$-HDL (i.e. small-sized HDL particles) and lower concentration of HDL$_{2b}$ (i.e. larger-HDL particles) (Yang et al 2005). Although we have not determined the HDL subclasses, our findings of the increased TG and decreased HDL-C levels suggest a larger production of smaller-sized HDL particles, altered reverse cholesterol transport and abnormal HDL production in our patients.

In contrast to previous reports of the altered cholesterol and LDL-C values in major depression (Maes et al., 1997), and bipolar disorders (Ghaemi et al., 2000; Atmaca et al., 2002; Cassidi and Carroll, 2002; Pae et al., 2004; Sagud et al., 2007), we have found similar serum cholesterol and LDL-C levels in patients and control subjects. Possible explanation for the discrepancies among studies might be sought in a variety of factors, like sex, medication status (Maes et al., 1997), decreased appetite/weight loss (Boston et al., 1996), or suicide attempts (Marcinko et al., 2007). Since our study included medication-free female subjects who were not suicidal, and their BMI did not differ between groups, our results agree with the suggestion that cholesterol levels could not be biological marker for major depression (Oxenkrug et al., 1983). In addition, our results obtained in medication free patients suggest that both cholesterol and LDL-C levels are not related to diagnostic entities such as major depression or bipolar disorder. The differences in the lipid profile among studies might be related to the diverse medication status. Namely, it has been reported that treatment with antidepressants (Maes et al., 1997), and psychoactive drugs (Glueck et al., 1994), significantly decreased both serum cholesterol and HDL-C levels in patients with major depression, or affective disorders. Numerous psychoactive drugs were shown to influence lipid levels: valproate reduced cholesterol levels (Bowden and Singh, 2005), carbamazepine increased

cholesterol, LDL-C and HDL-C levels (Weisler et al., 2005), while antipsychotic drugs increased cholesterol, TG and LDL-C levels (Saari et al., 2004). Therefore, the comparison of cholesterol levels in patients receiving pharmacological treatment and medication-free healthy controls (Glueck et al., 1994) is questionable.

HDL-C has a role in the reverse cholesterol transport and complex cholesterol homeostasis, processes important in the protection of the cardiovascular system (Norata et al., 2006; Sampietro et al., 2006). The results of our study, showing low HDL-C and high TG levels, suggest that patients with mood disorders are at higher risk for the development of cardiovascular disorders (Lesperance et al., 1996; Polk and Naqui, 2005). Since we have also found that mean HDL-C values in our female patients with mania, bipolar and major depression were within the values associated with the greatest risk for development of coronary heart disease (Wilson et al., 1998; Franceschini, 2001), these results recommend that our patients should be further followed up.

The limitations of the study were that the data on the physical activity, alcohol and dietary habits were not collected. In addition, we did not measure HDL-C subclasses (Yang et al 2005).

In conclusion, our data showed an inverse relationship between HDL-C and TG levels in patients with mood disorders, particularly in those with bipolar disorder (in a manic or a depressive phase). Due to the cross-sectional design, it is not possible to conclude whether low HDL-C levels and high atherogenic index contributed to a vulnerability to develop affective disorders, or low HDL-C levels occurred during the course of mood disorders. Since low HDL-C and increased atherogenic index are the risk factors for development of coronary heart disease, further investigations of lipid metabolism in affective disorders are warranted.

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Legends to figures

Fig 1. Serum HDL-C levels in healthy controls, patients with major depressive disorders and patients with bipolar disorders in manic or depressive episodes. Each column represents mean ± SD. Number of subjects is given in brackets.

*P<0.001 vs. healthy controls (ANOVA and Tukey's test)

Fig 2. Serum TG levels in healthy controls, patients with major depressive disorders and patients with bipolar disorders in manic or depressive episodes. Each column represents mean ± SD. Number of subjects is given in brackets.

*P =0.048 vs. major depression; **P=0.007 vs. healthy controls;

*** P<0.001 vs. healthy controls (ANOVA and Tukey's test)

Table 1. Demographic characteristics of patients with bipolar disorder (in a manic and a depressed phase), patients with major depression, and healthy controls. Data are presented as means ± SD. The number of subjects is given in breackets.

	Bipolar disorder		Major	*Healthy*
	Manic episode (22)	Depressive episode (19)	depressive Disorder (34)	*Controls (50)*
Age (years)	48.5 ± 13.2	44.1 ± 12.9	50.1 ± 6.6	*44.7± 12.8*
BMI (kg/m^2)	24.7 ± 4.5	23.3 ± 2.4	24.3 ± 2.2	*24.0 ± 4.5*
YMRS (scores)	26.1 ± 6.0			
HAMD (scores)	5.7 ± 1.6	27.3 ± 4.2	26.1 ± 2.2	
Disorder duration (years)	9.4 ± 9.6	12.5 ± 9.8	12.7 ± 10.4	
Current episode duration (days)	10.4 ± 11.3	4.2 ± 3.0	3.2 ± 1.5	
Number of prior manic episodes	5.2 ± 7.5	4.6 ± 5.8		
Number of prior depressive episodes	*6.7 ± 9.2*	*7.9 ± 7.8*	*3.1 ± 2.9*	

Table 2. Serum cholesterol, LDL-C levels and atherogenic index (cholesterol/HDL-C and LDL-C/HDL-C ratio) in healthy controls, patients with major depressive disorders, and patients with bipolar disorders in manic or depressive episodes. Results are expressed as means ± SD. Number of subjects is given in brackets.

	Cholesterol (mmol/L)	LDL-C (mmol/L)	*Atherogenic index*	
			Cholesterol/HDL-C	*LDL-C/HDL-C*
Healthy controls (50)	5.43 ± 1.05	3.39 ± 0.68	3.34 ± 0.93	*2.11 ± 0.69*
Major depression (34)	5.17 ±0,90	3.43 ±0.77	4.55 ±0,96*	*3.02 ±0.77**
Bipolar disorder in:				
- manic episode (22)	5.39 ± 1.27	3.68 ± 0.94	4.62 ± 1.29*	*3.26 ± 1.33**
-depressive episode (19)	5.43 ± 0.58	3.79 ±0.56	5.49 ± 1.24*,**,***	*3.80 ±0.67*,#*
ANOVA (df = 3, 121)				
F	0.503	1.899	22.764	*22.250*
P	*0.681*	*0.133*	*<0.001*	*<0.001*

**P*<0.000 vs. corresponding ratio in healthy controls; ***P*<0.045 vs. cholesterol/HDL-C ratio in bipolar disorder in manic episode ****P*<0.012 vs. cholesterol/HDL-C ratio in major depression # *P*<0.010 vs. LDL-C/HDL-C ratio in major depression (ANOVA followed by Tukey's test)

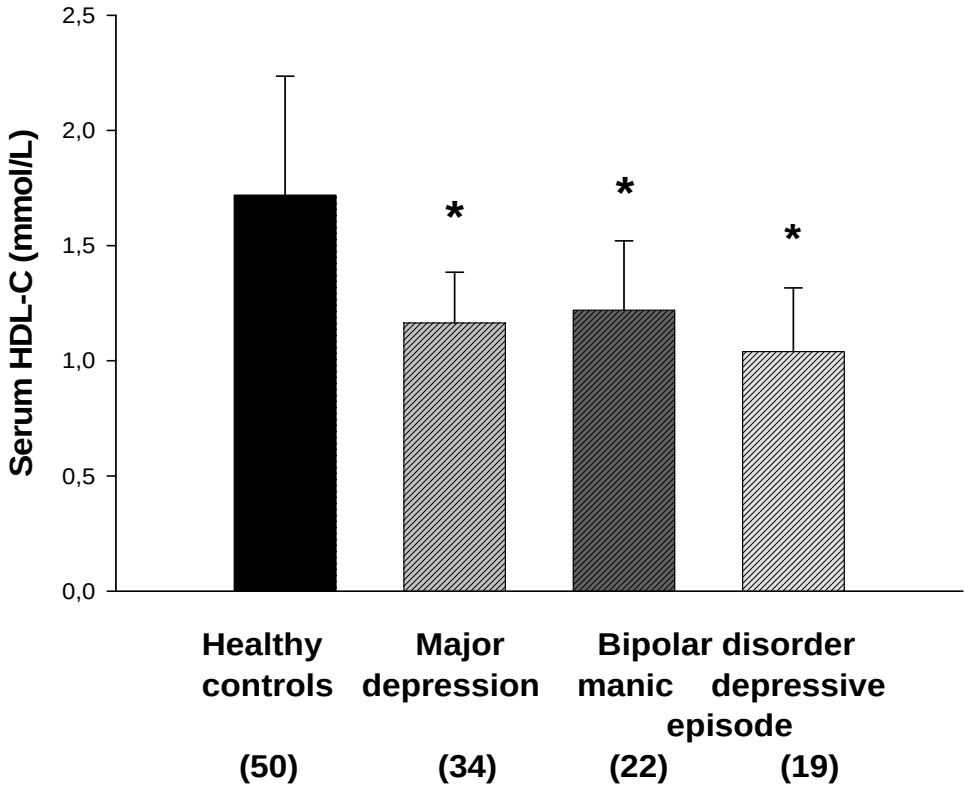
2,5
2,0
1,5
1,0
0,5
0,0
Serum HDL-C (mmol/L)
*
*
*
Healthy controls
Major depression
Bipolar disorder manic
depressive episode
(50)
(34)
(22)
(19)

Fig 1.

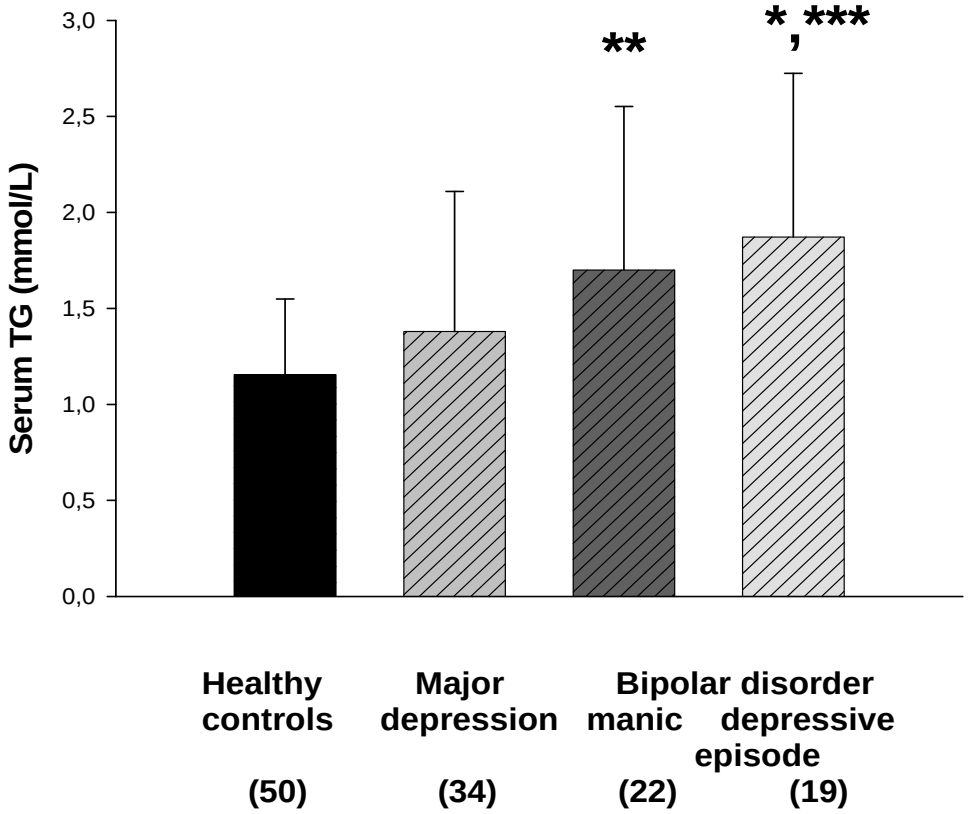
Serum TG (mmol/L)
3,0
2,5
2,0
1,5
1,0
0,5
0,0
**
*, ***
Healthy controls
(50)
Major depression
(34)
Bipolar disorder
manic
depressive episode
(22)
(19)

Fig.2.