HYPERLIPIDEMY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER IS ASSOCIATED WITH LESS SEVERE DEPRESSIVE SYMPTOMS

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Summary

Introduction. There is a high comorbidity of depression and cardiovascular disease which implicates course and prognosis of both disorders. Accidentally discovered correlation between low cholesterol and suicidal behavior in non-depressed population triggered robust interesting on this issue in depression. Major depressive disorder (MDD) patients display disturbed lipoprotein pattern. It was hypothesized that cholesterol depletion counteract 5-HT(7) receptor-mediated intracellular signaling in the central nervous system which can result in depressive symptoms onset.
Aim. We aimed to assess the possible correlation between blood lipids (total cholesterol (TCh), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG)) and basic depression characteristics: current age, age at onset, disease duration, number of hospitalization, number of suicide attempts and HDRS(17) rating.
Material and methods. Thirty eight MDD patients admitted to the psychiatry ward were included into the study and evaluated for serum lipids levels, body mass index (BMI) and depression severity on Hamilton Rating Scale for Depression-17 (HRSD(17)). Patients with currently disturbed lipid serum levels (TCh > 200mg/dL or HDL < 35mg/dL or HDL < 23% or LDL > 150 mg/dL or TG > 190 mg/dL) or who had been already treated with statins were considered hyperlipidemic.
Results. There were no differences in basic depression characteristics, BMI and lipids serum concentrations when compared males and females. We found no significant correlation between BMI and basic depression characteristics. Blood lipids also showed no significant correlation, except for LDL. LDL concentrations were significantly higher in patients with longer disease duration (R = 0.41, p = 0.010). Patients with mixed hyperlipidemia scored significantly lover on HDRS(17) (Z = -2.05, p = 0.040).
Conclusions. We can carefully conclude that not only cholesterol, but also its fractions and triglycerides may impact on depression severity. Currently depressed patients, especially with less severe depressive symptoms, should be a particular subject of cardiovascular preventive strategies.

Key words: depression, cardiovascular disorder, blood lipids

INTRODUCTION

There is a high comorbidity of depression and cardiovascular disease which implicates course and prognosis of both disorders (1). First, depression can seriously influence final clinical outcome in the light of being an independent risk factor for mortality in patients with coronary heart disease (CHD) (2). Second, depressed patients suffering from general somatic disorders are more likely than non-depressed patients to commit suicide, be non-concordant with treatment regimens, have greater somatic symptoms and disability, have a poorer quality of life and a higher rate of non-suicide-related deaths (3). There are few mechanisms explaining aetiological relationship between depression and cardiovascular disease, including: hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and cortisol elevation; decreased heart rate variability; elevated plasma levels of pro-inflammatory cytokines leading to atherosclerosis; platelet activation and hypercoagulability (4). Elevated pro-inflammatory cytokines and dyslipidemia act together while building atherosclerotic plate. Hypercholesterolemia, one of traditional cardiovascular risk factors (serum cholesterol levels over 200 mg/dL) (5), has been described as correlated with lower suicide risk in non-depressed population. In 1990 Muldoon et al. (6) found that reduction of cholesterol concentrations in patients with cancer resulted in significant increase in deaths not related to illness (deaths from accidents, suicide, violence). Disturbed lipid pattern and its significance in depression was described in depression with contradictory results. Some researches confirmed correlation between blood lipids and depression severity or suicide attempts, other did not (7).

Lipids, including cholesterol, are significant components of cell membrane and membrane receptors. It was hypothesized that cholesterol depletion counteract

serotonin – receptor binding in the central nervous system which may impact on depression symptoms onset. Sjögren et al. (8) examined the effects of cholesterol depletion on serotonin (5-HT) binding and signaling via 5-hydroxytryptamine (7) (5-HT) (7) receptors in stably transfected HeLa cells. The study demonstrated that cholesterol depletion decreases binding of both agonist and antagonist radioligands to 5-HT(7) receptors and counteract 5-HT(7) receptor-mediated intracellular signaling. Singh et al. (9) shown that the ligand binding activity of the hippocampal serotonin(1A) receptor is reduced upon cholesterol depletion and could be restored upon replenishment with cholesterol.

Analysis of sensitivity of the serotonin(1A) receptor to thermal deactivation, pH, and proteolytic digestion in control, cholesterol-depleted and cholesterol-enriched membranes comprehensively demonstrate that membrane cholesterol stabilizes the serotonin(1A) receptor (10).

We enrolled to our study major depressive disorder (MDD) patients and aimed to assess the possible correlation between blood lipids (total cholesterol (TCh), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG)) and current age, age at onset, disease duration, number of hospitalization, number of suicide attempts and HDRS(17) rating.

MATERIAL AND METHODS

Subjects

We enrolled 38 MDD patients (20 males, 18 females), aged 51.29 ± 11.55 (mean ± SD), admitted to a psychiatric ward between 2008 and 2010 for a treatment of depression. Patients fulfilled diagnostic criteria for MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (11). Written informed consent was obtained from all the participants of the study. The study protocol had been approved by the Local Bioethics Committee No. RNN/126/13/KB.

The patients were recruited for this study during the first week of hospitalization, just before or at the very beginning of SSRI treatment (first 2-3 days of treatment).

Basic depression characteristics of the study group (current age, age at depression onset, disease duration, number of hospitalization, number of suicide attempts, depression severity assessed with Hamilton Rating Scale for Depression-17 (HDRS(17)) are listed in table 1. Patients scored on HDRS(17) between 8 and 30 points (slight to very severe depression). Eleven patients (28.95%) confirmed family history of depression.

The mean BMI, serum lipids concentrations (TCh, HDL, LDL, TG) are listed in table 1. Twenty two patients were hyperlipidemic (57.89%). Nine of them were treated with 20 mg simvastatin/day for at least 3 months. Even though blood lipids were currently disturbed. The major limitation of this study is lack of the control group.

Depression severity rating

Depression severity was measured on admission with HRSD(17). The highest score in HRSD(17) is 52 points. Patients scoring between 0 and 7 points have no depression; 8-12 points – slight depression; 13-17 points – moderate depression; 18-29 points – severe depression; 30-52 points – very severe depression (12, 13).

Lipid serum levels assessment

Lipid serum levels (TCh, LDL, HDL, TG) were measured during the first week of hospitalization. Peripheral blood samples were drawn in the morning, between 7.00-9.00 AM after an all night fast. They were centrifuged and lipids were measured with enzymatic colorimetric method on the instrument Cobas Integra 400 plus of the Roche Diagnostics company. A reference values for the local laboratory were for TCh: 140-200 mg/dL; HDL ≥ 35 mg/dL; HDL ≥ 23%; LDL ≤ 150 mg/dL; TG: 60-190 mg/dL. Patients with currently disturbed lipid serum levels (TCh > 200 mg/dL or HDL < 35 mg/dL or HDL < 23% or LDL > 150 mg/dL or TG > 190 mg/dL) or who had been already treated with statins were considered hyperlipidemic.

Statistical analysis

All data analyses were performed in Statistica (version 10.0). The results were presented as percentages (%) or means with standard deviations (± SD). Types of measurements were selected after the analysis of the variables tested, which showed no normal distribution. P-values less than 0.05 were considered to be significant. We used Mann-Whitney U-test: 1. to determine differences between current age, age at onset, disease duration, number of hospitalization, number of suicide attempts, HDRS(17) rating, body mass index (BMI) and serum lipid indices in male and female MDD patients; 2. to determine differences between current age, age at onset, disease duration, number of hospitalization, number of suicide attempts, HDRS(17) rating and hyperlipidemic and nonhyperlipidemic subgroups.

To evaluate the correlation between blood lipid levels and current age, age at onset, disease duration, number of hospitalization, number of suicide attempts, HDRS(17) rating, Spearman's rank correlation coefficients were estimated.

RESULTS

Male and female patients did not differ significantly according to current age, age at onset, disease duration, number of hospitalization, number of suicide attempts, HDRS(17) rating, BMI and lipid serum concentrations (tab. 1).

Table 1. Basic characteristics of the MDD patients (N = 38).

	M ± SD	Samples (n (%))	Significance (M versus F)
Sex			
M		20 (52.63)	
F		18 (47.37)	
Current age	51.29 ± 11.55		Z = 0.89; p = 0.373
Age at onset	42.92 ± 12.16		Z = 0.10; p = 0.919
Disease duration	8.55 ± 8.52		Z = 0.91; p = 0.365
Total number of hospitalization	2.61 ± 1.99		Z = 0.09; p = 0.93
Number of suicide attempts	0.55 ± 1.03		Z = -0.63; p = 0.530
Presence of family history of depression		11 (28.95)	
HDRS(17)	18.95 ± 5.90 points Range 8-30 points		Z = -0.91; p = 0.365
Hyperlipidemia		22 (57.89)	
BMI [kg/m2]	27.30 ± 5.46 Range 17.91-42.23		Z = -0.47; p = 0.640
TCh [mg/dl]	207.29 ± 45.46		Z = -0.94; p = 0.350
HDL [mg/dl]	51.45 ± 16.11		Z = 0.34; p = 0.737
HDL [%]	25.42 ± 8.29		Z = 0.01; p = 0.988
LDL [mg/dl]	126.13 ± 37.43		Z = -0.48; p = 0.630
TG [mg/dl]	150.79 ± 80.67		Z = -1.40; p = 0.161

MDD – major depressive disorder; M – male patients; F – female patients; HDRS(17) – 17-itemic Hamilton Rating Scale for Depression; BMI – body mass index; TCh – total cholesterol; LDL – low density lipoprotein; HDL – high density lipoprotein; TG – triglycerides; M – arithmetic mean; ± SD – standard deviation; Z – Mann-Whitney U-test; p – level of statistical significance.

We found no significant correlation between BMI and basic depression characteristics: current age, age at onset, disease duration, number of hospitalization, number of suicide attempts, HDRS(17) rating (tab. 2). Blood lipids also showed no significant correlation, except for LDL. LDL concentrations were significantly higher in patients with longer disease duration (R = 0.41, p = 0.010) (tab. 2).

Hyperlipidemic patients (n = 22) scored significantly lower on HDRS(17) (Z = -2.05, p = 0.040) (tab. 3).

DISCUSSION

Here we found a significant correlation between LDL and basic depression characteristic. Higher LDL was seen in patients with longer disease duration. Other blood lipids displayed no significant correlation with basic depression characteristics. However, hyperlipidemic MDD patients scored lower on HDRS(17). Taken together, blood lipids displayed no significant correlation with depression severity when analyzed separately, but the hyperlipidemic subgroup appeared to have less severe depression. We can carefully conclude that not only cholesterol, but also its fractions and triglycerides may be related to depression severity. Van Reedt Dortland (14) found different lipid pattern in current MDD versus remitted MDD and controls. Patients with active depression symptoms had lower HDL cholesterol and higher triglyceride level. The value of such findings and theirs clinical significance requires further investigation, but indicates that currently depressed MDD patients with active depressive symptoms have more atherogenic lipid profile than those in remission. Our study showed that MDD patients with less severe depression are hyperlipidemic. Theoretically it would be possible to suspect that hypercholesterolemy plays a protective role against more severe depression in the light of cholesterol – serotonin receptor interaction, but here a complex hyperlipidemy was associated with less severe depression. In our opinion it can be related to the different lifestyle factors that can be developed by currently less and more depressed patients. The psychopathology of MDD depression contains symptoms that create lifestyle behavior being of higher cardiovascular risk. MDD patients are typically of decreased energy and motor activity, but

Table 2. BMI and lipids vs basic depression characteristics in MMD patients (N = 38).

	BMI	TCh	HDL [mg/dl]	HDL [%]	LDL [mg/dl]	TG [mg/dl]
Current age	R = -0.15 p = 0.383	R = 0.01 p = 0.974	R = -0.04 p = 0.792	R = -0.05 p = 0.747	R = 0.11 p = 0.517	R = -0.18 p = 0.292
Age at onset	R = 0.09 p = 0.580	R = -0.06 p = 0.699	R = -0.09 p = 0.597	R = 0.08 p = 0.628	R = -0.06 p = 0.737	R = -0.02 p = 0.929
Disease duration	R = -0.03 p = 0.874	R = 0.30 p = 0.066	R = 0.00 p = 0.994	R = -0.30 p = 0.063	R = 0.41 p = 0.010	R = -0.06 p = 0.741
Number of suicide attempts	R = 0.20 p = 0.239	R = -0.03 p = 0.881	R = -0.30 p = 0.068	R = -0.14 p = 0.418	R = 0.02 p = 0.895	R = 0.24 p = 0.142
Number of hospitalization	R = 0.31 p = 0.059	R = -0.02 p = 0.908	R = -0.24 p = 0.147	R = -0.26 p = 0.113	R = 0.07 p = 0.662	R = 0.10 p = 0.534
HDRS	R = -0.18 p = 0.288	R = -0.15 p = 0.385	R = 0.15 p = 0.361	R = 0.17 p = 0.304	R = -0.25 p = 0.131	R = 0.07 p = 0.659

MDD – major depressive disorder; HDRS(17) – 17-itemic Hamilton Rating Scale for Depression; BMI – body mass index; TCh – total cholesterol; LDL – low density lipoprotein; HDL – high density lipoprotein; TG – triglycerides; M – arithmetic mean; ± SD – standard deviation; p – level of statistical significance; R – Spearman's rank correlation coefficient.

Table 3. The comparison of basic depression characteristics in hyperlipidemic (n = 22) vs nonhyperlipidemic (n = 16) subgroups of MDD patients.

	Current age	Age at onset	Disease duration	Number of suicide attempts	Number of hospitalization	HDRS
Hyperlipidemic vs non-hyperlipidemic MDD patients	Z = 1.43 p = 0.152	Z = 1.64 p = 0.101	Z = 0.18 p = 0.859	Z = 0.77 p = 0.442	Z = 0.25 p = 0.802	Z = -2.05 p = 0.040*

*Hyperlipidemic patients scored on HDRS(17) 17.23 ± 5.67 points (range 8-27)
Non-hyperlipidemic patients scored on HDRS(17) 21.31 ± 5.51 points (range 8-30)
MDD – major depressive disorder; HDRS(17) – 17-itemic Hamilton Rating Scale for Depression; Z – Mann-Whitney U-test; p – level of statistical significance.

more severe depression is connected with higher irritability, increased motor activity and even agitation, high motor activity with anxiety. Our patients with less severe depression were hyperlipidemic. We indicate that the different psychopathology of less and more depressed patients can influence blood lipids concentration in the light of different motor activity and should be taken into consideration when discussing the results of similar studies.

It was hypothesized that the mechanism underlying association between low cholesterol, depression and suicidal behavior is that low cholesterol counteracts serotonin-receptor actions in the central nervous system, like it was shown in HeLa cells by Sjögren et al. (8). However Engström et al. (15) determined serum lipids and cerebrospinal fluid monoamine metabolites in 72 suicide attempters and could not give much no support for this hypothesis in humans. We found no correlation between blood lipids and suicide behavior. However only 11 (28.95%) patients had a history of suicide attempts. In depressed populations comprising only patients who have attempted suicide like in 51 subjects assessed by Papadopoulou et al. (16), TCh levels after a suicide attempt were lower than healthy controls and remained low in follow-up, independently from the severity of psychopathology. Deisenhammer et al. (17) assessed 110 alcohol-dependent patients. Patients who had attempted suicide at least once in their life had higher serum triglyceride levels. None of our patients was alcohol-dependent and we did not found association between triglycerides and suicide attempts. It is necessary to add that alcohol-dependence remains a suicide risk factor itself.

Nine MDD patients were on statin treatment. Eight of them have never attempted a suicide, one woman has attempted it 4 times in the lifetime. No other lipid lowering treatment was used in our MDD group. It is obviously to small sample to conclude possible correlation between statin treatment and suicide behavior. Accidentally founded correlation between low cholesterol and increased suicide risk made even a potentially dangerous suggestion to suspend treatment with statins (7). However metaanalysis of the nonillness mortality outcomes of large, randomised clinical trials of cholesterol

lowering treatments did not support the hypothesis that statins are associated with an increased risk of suicide (18). Yang et al. (19) analysed 458 depressed and 105 patients with suicidal behavior. They have indicated that exposure to lipid lowering drugs does not increase the risk of depression. It was even shown that current statin treatment was associated with reduced risk of depression. It was especially prominent in patients with 01 year or longer duration of statin treatment. Our patients have been treated with simvastatin (20 mg per day) for at least 3 months but not longer than 1 year. Callreus et al. (20) analysed 743 cases of completed suicide and found no correlation between statin treatment and suicide risk.

CONCLUSION

We can carefully conclude that not only cholesterol, but also its fractions and triglycerides may be correlated with depression severity.

Currently depressed patients, especially with less severe depressive symptoms, should be a particular subject of cardiovascular preventive strategies. □

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